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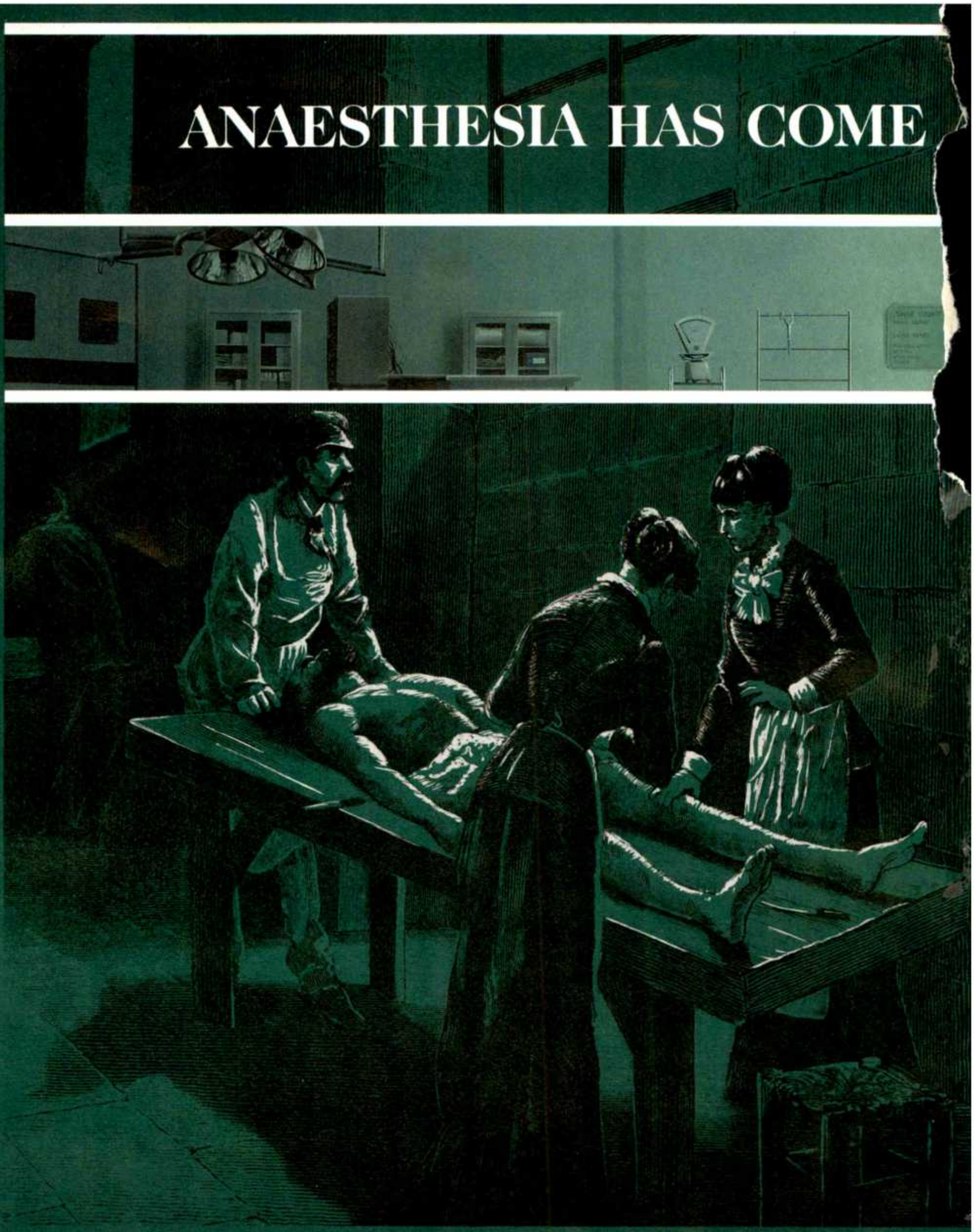

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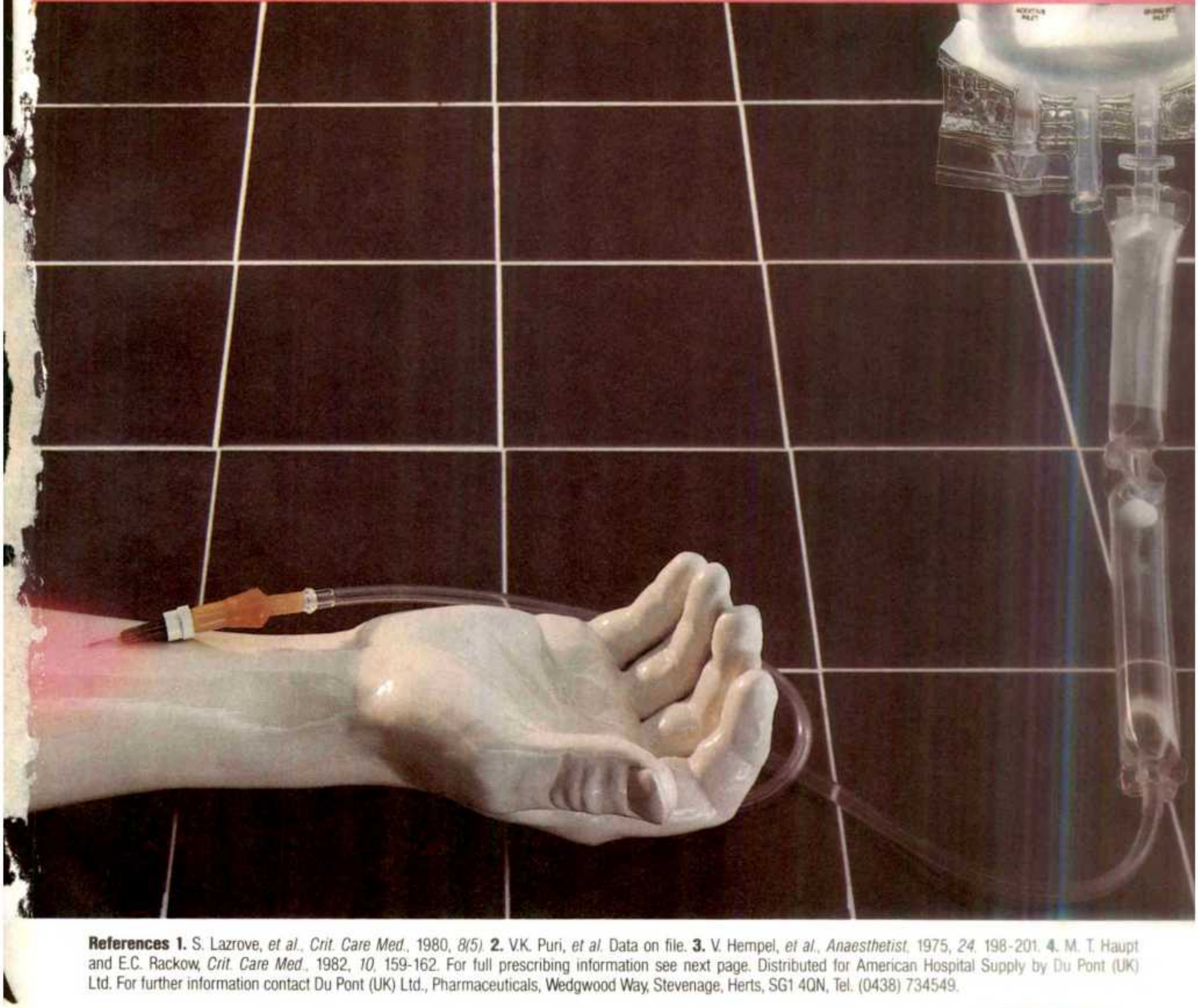

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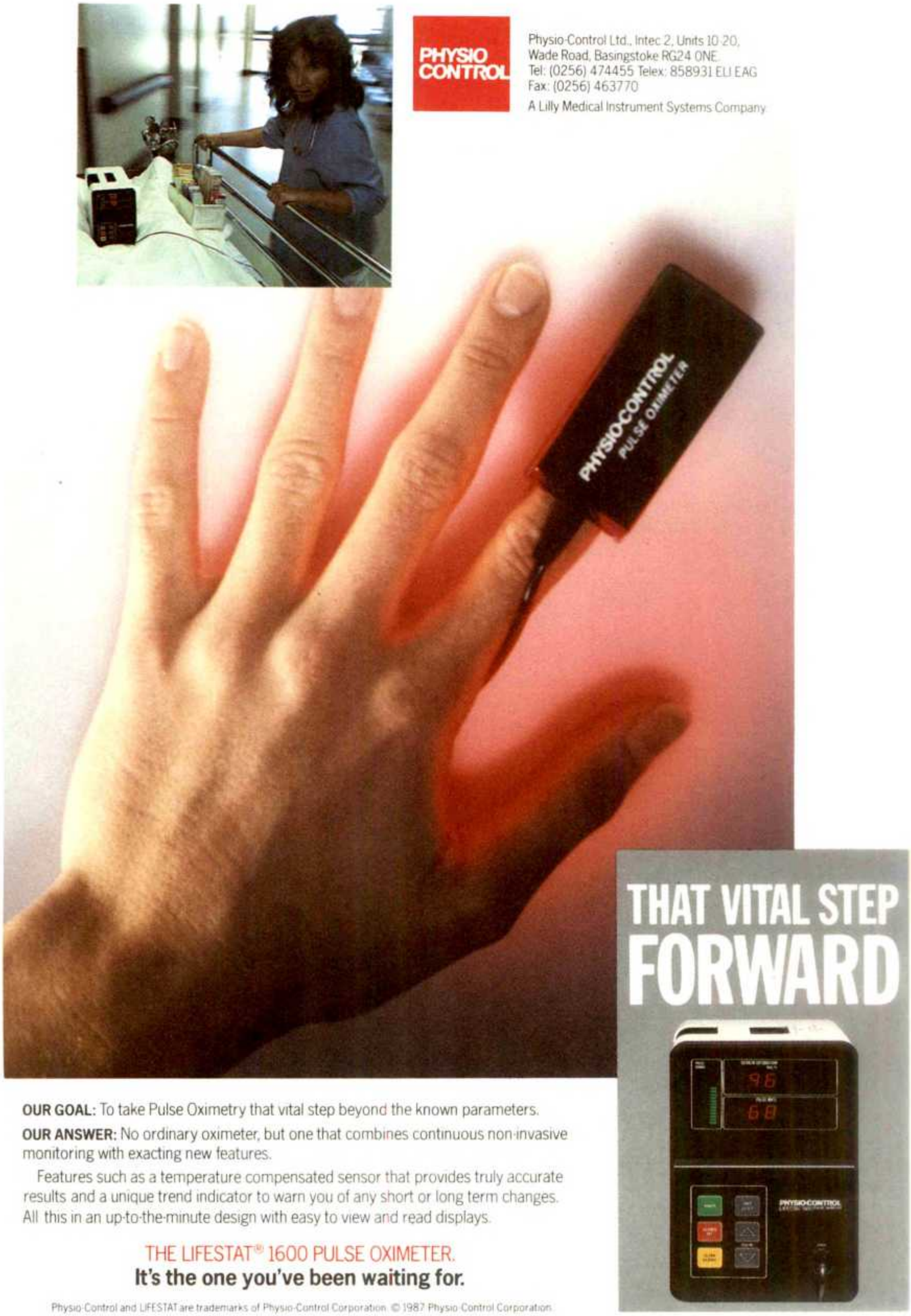

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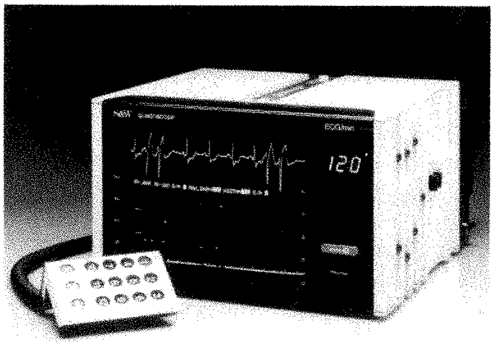

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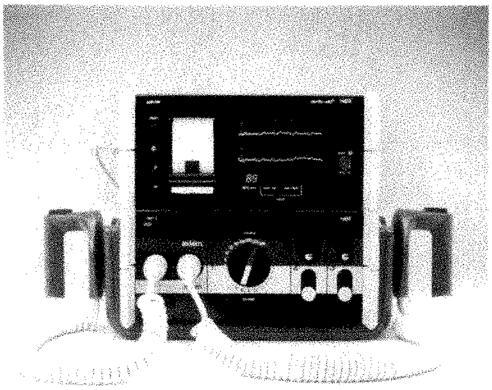

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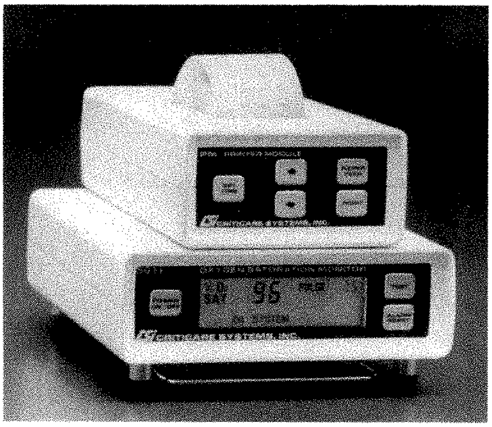

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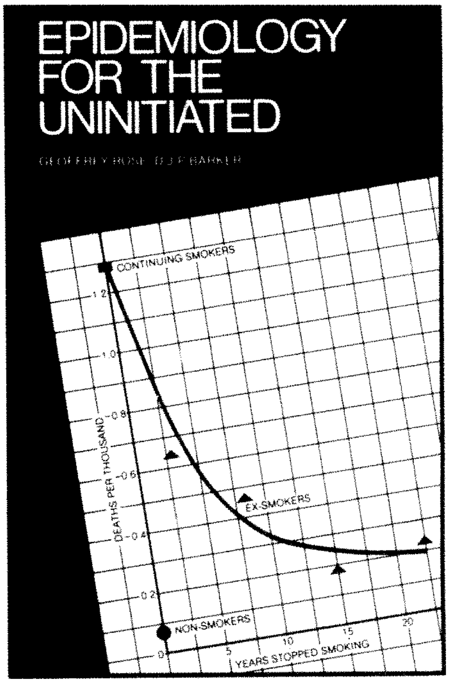

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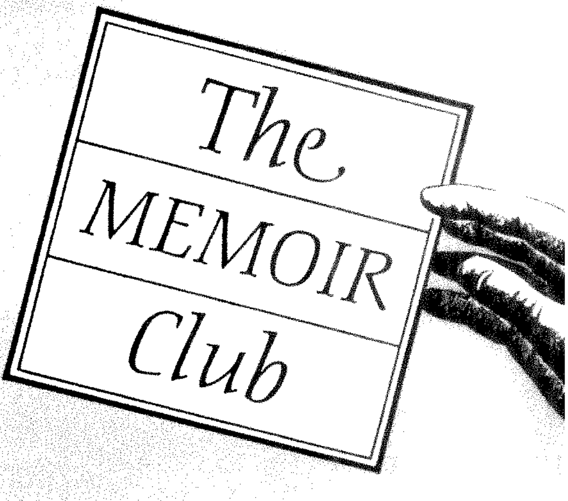

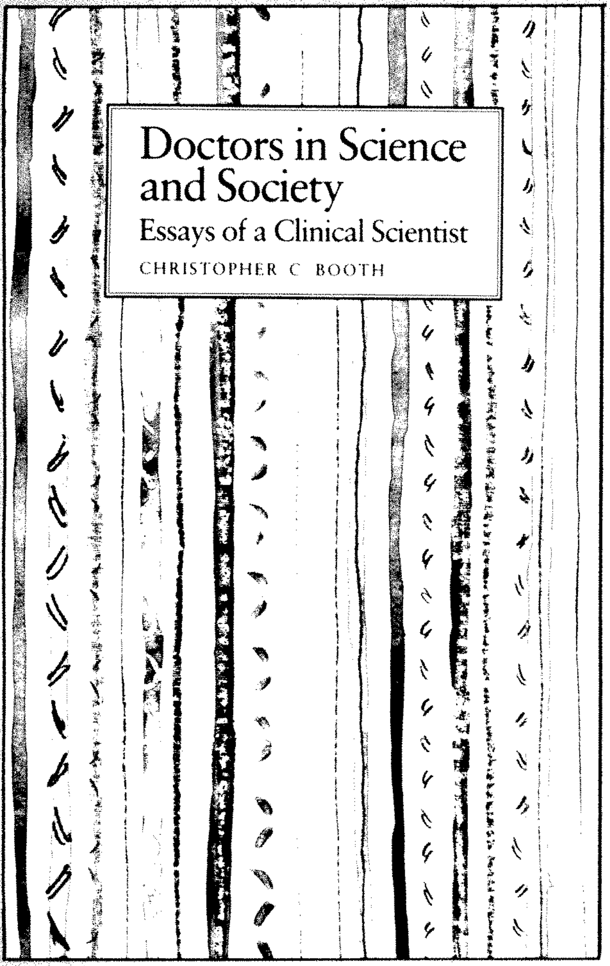
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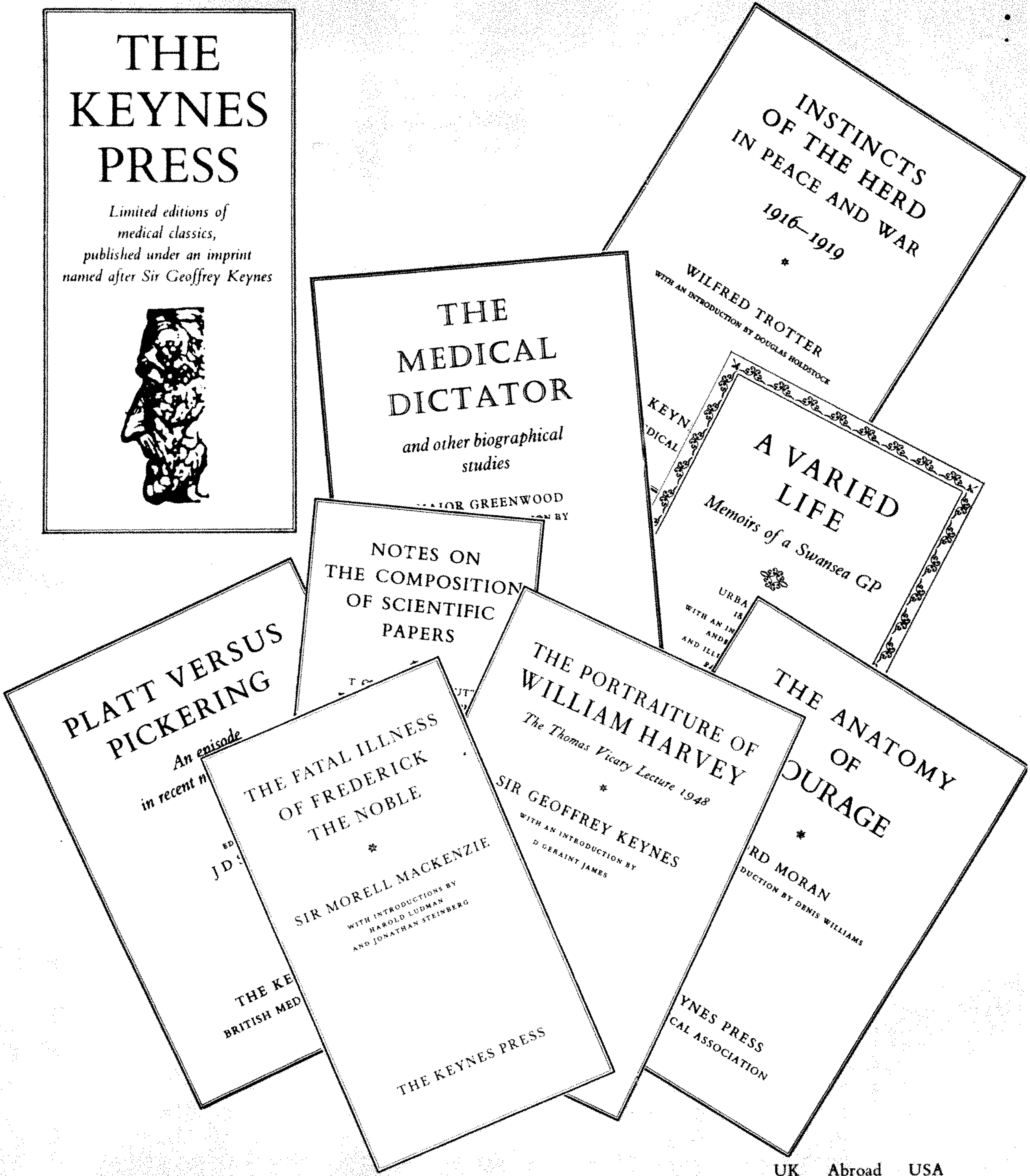
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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 59, No. 10 OCTOBER 1987

EDITORIALS

MONITORING: BANE OR BLESSING?

Imagine, if you will, a typical district general hospital. Identical major operations are being performed on similar patients in adjoining operating theatres. In the one the senior anaesthetist, using his sole, unvarying technique which has served him well for more than 20 years, eschews electronic aids and sits constantly at the head of the operating table taking the heart rate and arterial pressure manually every 5 minutes without fail. In the other, the newest consultant gives an anaesthetic individually "tailored" to his perception of the patient's needs. Surrounded by electronic monitoring equipment the accurate function of which he checks frequently, he responds instantly to each subtle variation in physiological status with an adjustment in therapy. The first patient returns to the general ward where the experienced sister gives him a large dose of "Omnopon" and places him close to the desk, under her watchful eye. The other goes to the Intensive Care Unit where his bodily functions are scrutinized throughout the day and night. Both patients survive and go home.

Which patient has received the best anaesthetic? Has the monitoring and the "fine-tuning" of the physiological status that it makes possible been of any value to the second patient? Which patient received the "safer" anaesthetic? Such questions lie at the root of the controversy over the value of monitoring and are, as yet unanswered. The only claim that could be made with any confidence is that the second anaesthetic was more expensive than the first.

New technology has brought great advances in the field of monitoring and further developments are promised. Great pressure is exerted on the profession to purchase such instruments with promises of "better" and "safer" anaesthesia. Much of this pressure is fuelled by the litigation experience of the United States, where the malpractice insurance fees add $53 to the cost of each anaesthetic (Eichhorn et al., 1986). A comparable figure for the United Kingdom would be 70p–£1. Adoption of the new technology must be accompanied by a reappraisal of the purposes, advantages and disadvantages of monitoring, rather than an uncritical acceptance.

The purpose of monitoring is two-fold. First, it serves to assist the anaesthetist to control the depth of anaesthesia and the degree of "physiological trespass". It can help to relieve the tedium of prolonged operations and frees the anaesthetist to perform other tasks. Second, it should warn of disasters, many of which occur very infrequently and are thus not expected. The death rate from anaesthesia in the U.K. has been estimated at 1:10000 anaesthetics (Lunn and Mushin, 1982); thus the average anaesthetist is likely to only experience one or two such incidents in a working lifetime.

The monitoring techniques that are most widely used, electrocardiography and non-invasive measurement of arterial pressure, are primarily of value for the control of anaesthesia and are of little value for the early detection of disaster (Weingarten, 1986). In any critical incident, time elapses between the detection of the problem, the identification of the cause and its correction, during which damage to the patient may occur. Delay in any of these phases increases the likelihood of injury. Thus early detection and a prompt response are both important if any disaster is to be averted.

It is widely recognized that the most effective monitor is the constant presence of a skilled, attentive anaesthetist. The Harvard group and the American Society of Anesthesiologists have recognized this by according it the first position in their recently published standards for minimum monitoring (ASA, 1986; Eichhorn et al., 1986). One of the hazards of monitoring is that it may give a false sense of security and discourage the anaesthetist from maintaining close physical contact with the patient. It is incumbent on all those responsible for the training of novice anaesthetists to stress the absolute necessity of this practice. A short length of string linking the patient and his anaesthetist is a valuable symbol that deserves wider use, at least in the early part of training!

However, it must not be thought that "eternal vigilance" is the only monitor we need. Clinical investigation and experience show that the human senses can not detect hypoxia (Comroe and Bothelo, 1947) or the adequacy of ventilation (Semmes et al., 1985) with sufficient sensitivity or reliability. The use of monitors which can detect these factors, such as the capnograph and pulse oximeter, is thus not supplanting but extending our vigilance, supplementing the deficiencies in our clinical ability.

Oxygen analysers to monitor the inspired gases and ventilator alarms are widely advocated to improve the safety of anaesthesia (Franklin, 1979; Marks, 1983). However, they provide no physiological information and are thus unlikely to be scrutinized often enough to ensure accuracy and continued function. They are best regarded as solely monitors of anaesthetic machine function, since they give no guarantee of the patient's well being (Weingarten, 1986).

We should also question the times during which we use monitors. Current practice is to establish monitoring only after the patient has been transferred from the induction room to the operating theatre and to discontinue it before the move to the recovery area. The logic of this practice is questionable, since many anaesthetic disasters occur during induction or recovery and during periods of change such as the movement from one area to another. Monitoring, then, needs to be available in these high risk areas and to be portable. We may also need to reconsider our cherished induction rooms and induce anaesthesia in high risk patients in the operating theatre.

Used uncritically, monitoring may be at worst a bane and at best a mixed blessing. Used appropriately, it can be a blessing for both the control of anaesthesia and its safety. Appropriate monitoring is the rational use of devices, throughout the period of risk, that supplement or enhance our clinical skills rather than encouraging them to wither. By the adoption of such principles, the priorities for the acquisition of monitors can be determined and a rational allocation made of the available finance. The question of the cost effectiveness of monitoring for patient safety will only be satisfactorily answered by observing the results of a consistent change in practice by a large group of anaesthetists working together. A code of practice for the United Kingdom, similar to the Harvard recommendations and those of the American Society of Anesthesiologists, and based upon a wide consensus is needed urgently.

C. D. Hanning

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ANTIBODY TO HALOTHANE-INDUCED LIVER ANTIGEN

Klatskin and Kimberg (1969) reported recurring fever and hepatitis associated with repeated exposure to halothane. Since then many authors have speculated on an immunological basis in the causation of halothane-associated hepatitis. Various (statistically weak) associations with presumed halothane hepatitis have included a previous history of drug allergy, eosinophilia, rash, arthralgia and liver–kidney microsomal (LKM) autoantibodies in serum. There can be little doubt that these, and related considerations, had a fundamental influence on the interpretation of data held by the U.K. Committee on Safety of Medicines on which the current recommendation on the interval between two halothane anaesthetics is based. What is certain is that severe liver injury associated with halothane is not a process of direct dose-related toxicity, but of idiosyncrasy.

The identification of an antibody which interacts with halothane-altered rabbit hepatocytes is the product of some 10 years of research by scientists at the Liver Unit of King's College Hospital, London. Their work has been one of the more interesting developments in the field of anaesthetic toxicity. Initially, the antigen complex used was derived from a crude homogenate of hepatocytes from rabbits exposed acutely to anaesthetic concentrations of halothane (Vergani et al., 1978). Later methods were refined to allow testing with an antigen known to be on the hepatocyte membrane (Vergani et al., 1980). The ELISA (enzyme linked immunosorbent assay) now used provides a faster, more reliably quantitative, test which has enabled the King's College group to screen samples from patients outside their own liver service (which, in the nature of things, concentrates on patients with fulminant hepatis necrosis). Thus in their report Kenna, Neuberger and Williams (p. 1286 of this issue) have information on patients with a wide spectrum of severity of halothane hepatitis, whereas previous reporting has been confined to those with fulminant hepatic failure.

The recurrence of the "halothane" antibody is of interest for two reasons. First, there is the possibility that the antibody is, itself, a factor in the liver injury. While it is generally held that the halothane molecule alone cannot be antigenic, a halothane–liver cell membrane moiety as an antigen, coated with antibody, may attract T-lymphocytes ("Killer Cells") as an intiating process in liver necrosis. Dienstag (1980) has warned against this view on the ground that such a mechanism would result in a very early antibody response and early onset of liver injury. In some patients, however, antibodies did not appear until several weeks after exposure to halothane. This suggests that they are secondary to liver damage.

The other important matter is that the detection of antibody might offer a specific indicator of halothane as the cause of postoperative liver injury—a great improvement over diagnosing halothane-associated hepatitis by a process of excluding other causes of liver damage. In this respect, the latest report is disappointing. In at least one-quarter of the patients with presumed halothane hepatitis, the antibody could not be found. It might be that binding of antibody to liver tissue results in its absence in detectable quantities from serum. It is also possible, of course, that these patients have a reason other than halothane for their liver injury. The sensitivity of the test may be deficient, although that seems unlikely. Last, it is possible that there is more than one type of liver lesion associated with halothane; if this argument is sustainable it could give further credence to the hypothesis that the antibody may precipitate hepatic necrosis.

There is no clear association between the presence of antibody and any other features documented in the patients with liver injury. For example, the occurrence of antibody was similar in cases of fulminant and less severe liver injury. Age, sex, severity of operation, previous anaesthetic history, biochemical data and time to onset of jaundice were poor predictors of severity of hepatitis and of the likelihood of antibody. While these studies are applauded, it must be clear that the value of the antibody test in diagnosis is limited.

A. A. Spence

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CEREBRAL BLOOD FLOW AND METABOLISM DURING ISOFLURANE-INDUCED HYPOTENSION IN PATIENTS SUBJECTED TO SURGERY FOR CEREBRAL ANEURYSMS

J. B. MADSEN, G. E. COLD, E. S. HANSEN, B. BARDRUM
AND C. KRUSE-LARSEN

Isoflurane decreases the cerebral metabolic rate for oxygen ($CMRo_2$) (Cucchiara, Theye and Michenfelder, 1974; Newberg, Milde and Michenfelder, 1983; Newman, Gelb and Lam, 1986); cerebral blood flow (CBF) is either unaltered (Todd and Drummond, 1984) or increased (Cucchiara, Theye and Michenfelder, 1974; Murphy et al., 1974; Eintrei, Leszniewski and Carlsson, 1985). Some controversy exists concerning the effects of isoflurane on intracranial pressure (ICP); in some studies little or no effect has been observed (Adams et al., 1981; Campkin, 1984); in a more recent study an increase in ICP was obtained (Grosslight et al., 1985). Comparative studies of the effects of halothane or isoflurane (Murphy et al., 1974; Todd and Drummond, 1984; Eintrei, Leszniewski and Carlsson, 1985) suggest that, although isoflurane has a less marked vasodilatory effect on cerebral blood vessels, it causes a more marked suppression of oxygen consumption (Todd and Drummond, 1984). During isoflurane-induced hypotension to a mean arterial pressure (MAP) of 40 mm Hg the concentrations, in cerebral tissue, of ATP, phosphocreatine, lactate and pyruvate did not change significantly, indicating the persistence of aerobic metabolism (Newberg, Milde and Michenfelder, 1984).

The aims of the present study were to determine the effects of isoflurane-induced hypotension — during craniotomy for cerebral aneurysm — on CBF and $CMRo_2$ during the pre-, per and post-hypotensive periods.

SUMMARY

Cerebral blood flow and cerebral metabolic rate for oxygen were measured during isoflurane-induced hypotension in 10 patients subjected to craniotomy for clipping of a cerebral aneurysm. Flow and metabolism were measured 5–13 days after the subarachnoid haemorrhage by a modification of the classical Kety–Schmidt technique using xenon-133 i.v. Anaesthesia was maintained with an inspired isoflurane concentration of 0.75% (plus 67% nitrous oxide in oxygen), during which CBF and $CMRo_2$ *were* 34.3 ± 2.1 *ml/100 g* min^{-1} *and* 2.32 ± 0.16 *ml/100 g* min^{-1} *at* Pa_{CO_2} 4.1 ± 0.1 *kPa (mean ± SEM). Controlled hypotension to an average MAP of 50–55 mm Hg was induced by increasing the dose of isoflurane, and maintained at an inspired concentration of* $2.2 \pm 0.2\%$. *This resulted in a significant decrease in* $CMRo_2$ *(to* 1.73 ± 0.16 *ml/100 g* min^{-1}*), while CBF was unchanged. After the clipping of the aneurysm the isoflurane concentration was reduced to 0.75%. There was a significant increase in CBF, although* $CMRo_2$ *was unchanged, compared with pre-hypotensive values. These changes might offer protection to brain tissue during periods of induced hypotension.*

PATIENTS AND METHODS

Patients

CBF and $CMRo_2$ were measured in 10 patients subjected to surgery for the elective clipping of a cerebral aneurysm during isoflurane-induced hypotension. The craniotomy was performed 5–13 days after the subarachnoid haemorrhage. The

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J. B. MADSEN, M.D., G. E. COLD, M.D., E. S. HANSEN, M.D. (Department of Anaesthesia); B. BARDRUM, M.D., C. KRUSE-LARSEN, M.D. (Department of Neurosurgery); Hvidovre Hospital, Kettegaards Alle 30, DK-2650 Hvidovre, Denmark.
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Correspondence to J.B.M. (Department of Anaesthesia).

mean age of the patients was 41 yr (range 30–62 yr) and the mean weight 67.5 kg (range 50–92 kg). All gave informed consent and the study was approved by the local scientific ethics committee. All the patients were awake and conscious without peripheral neurological deficits (Hunt and Hess grade I–II) (Hunt and Hess, 1968).

Anaesthesia

One hour before the induction of anaesthesia the patients were premedicated by mouth with diazepam 5 mg/25 kg body weight. Anaesthesia was induced with thiopentone 5–7 mg kg^{-1} i.v. supplemented with fentanyl 0.2 mg i.v. Pancuronium 0.10–0.15 mg kg^{-1} i.v. was administered. Isoflurane (inspired concentration 0.75%) was used to maintain anaesthesia, supplemented with 67% nitrous oxide in oxygen. Fentanyl 0.1 mg was given before skin incision. In three patients additional doses (2 mg) of pancuronium were administered during the anaesthetic to maintain neuromuscular blockade. Ventilation was controlled throughout (Servo ventilator 900 B, Siemens Elema, Sweden) and end-expiratory carbon dioxide concentration monitored (Siemens Elema, Sweden). The vaporizer (Dräger Technic AG, Lübeck, West Germany) was calibrated before the study. Mean arterial pressure (MAP) was monitored and recorded (Servigor, BBC Goerz, Austria). Arterial blood-gas tensions were measured (ABL 1, Radiometer, Denmark), and Pa_{O_2} was maintained greater than 100 mm Hg. Simultaneously with the opening of the dura, hypotension was induced by increasing the isoflurane concentration until MAP averaged 50–60 mm Hg. Shortly after clipping of the aneurysm, the isoflurane concentration was reduced to 0.75%.

Measurements of cerebral blood flow

In each patient three peroperative measurements of CBF were performed, before, during and after isoflurane-induced hypotension. Before surgery the internal jugular vein contralateral to the aneurysm was cannulated using the anterior approach, and a catheter was placed at the base of the skull (confirmed by x-ray). Simultaneously, a cannula was inserted to the dorsalis pedis or radial artery to permit direct pressure measuring and the aspiration of blood. Xenon-133, 3 mCi in saline was infused i.v. over a period of 20 min to obtain saturation of brain tissue.

Two-millilitre blood samples were drawn from the artery and the jugular vein at exact time intervals of 20 min during the saturation period and at 1, 2, 3, 4, 5, 7, 9, 11, 13, 15, 18, 20, 25 and 30 min during the desaturation period. The radioactivity in the samples was counted and the arterial and venous desaturation curves were drawn.

CBF was calculated using the height-over-area formula (CBF$_{30}$), and CMRo$_2$ from the product of CBF and the arterio–venous oxygen content difference ($Ca_{O_2} - Cv_{O_2}$), which was measured in triplicate during each flow (OSM-2, Radiometer, Denmark). This i.v. modification of the classical Kety–Schmidt method (Kety and Schmidt, 1948) has recently been described in detail (Astrup et al., 1984; Bendtsen et al., 1985). The first CBF measurement was performed about 1 h after the induction of anaesthesia. A 20-min period of stable hypotension at a constant inspiratory isoflurane concentration was allowed before the flow measurement was repeated. The third determination of CBF was undertaken about 30 min after reducing the inspired isoflurane concentration to 0.75%. The data are presented in the text and table I as mean ± SEM, and a P value < 0.05 was considered significant. The Wilcoxon test for paired data was used.

RESULTS

In all patients the operative conditions were excellent. There was no evidence of brain herniation; mannitol was not used. The patients recovered uneventfully and regained consciousness rapidly. One week and 1 month after the operation all the patients had recovered without neurological deficit. The desired level of hypotension was achieved 14 min (range 10–17 min) after the change in the isoflurane concentration. The level of hypotension was stable and only minor adjustments in isoflurane concentration were necessary. The average duration of hypotension was 62 min (range 36–117 min). During the posthypotensive period a stable MAP was achieved after 6.5 min (range 3–16 min).

During the prehypotensive period, CBF and CMRo$_2$ averaged 34.3 ± 2.1 ml/100 g min^{-1} and 2.32 ± 0.16 ml/100 g min^{-1} at MAP 74.5 ± 2.2 mm Hg and Pa_{CO_2} 4.1 ± 0.1 kPa. During the hypotensive period MAP averaged 54.6 ± 1.2 mm Hg and Pa_{CO_2} 3.97 ± 0.2 kPa. The isoflurane concentration was 2.2 ± 0.2%. A significant decrease in CMRo$_2$ was noted ($P < 0.05$)

(table I), while a non-significant increase in CBF was observed. After the clipping of the aneurysm the isoflurane concentration was returned to 0.75%. In comparison with the prehypotensive values, MAP and CMRo$_2$ were unchanged, whereas CBF was significantly greater ($P < 0.05$) (table I).

DISCUSSION

In patients with subarachnoid haemorrhage who would be classified as grade I–II according to the criteria of Hunt and Hess (1968), CBF and CMRo$_2$ were significantly decreased compared with values obtained in awake normal subjects (Voldby, Enevoldsen and Jensen, 1985a).

In a recent study of CBF and CMRo$_2$ during surgery for cerebral aneurysm in patients subjected to 1% isoflurane in an oxygen–air mixture, CBF and CMRo$_2$ were 49.1 ml/100 g min^{-1} and oxygen 2.0 ml/100 g min^{-1}, respectively, at MAP 78 mm Hg and Pa$_{CO_2}$ 4.4 kPa (Newman, Gelb and Lam, 1986). This difference in CBF compared with the present study might be caused by a difference in concentration in isoflurane (0.75% v. 1.0%); by the use of mannitol before induction in the cited study, since mannitol is known to increase CBF (Mendelow et al., 1985); because nitrous oxide was avoided; or because of a desaturation period of 15 min, compared with the 30 min used in the present study.

During the hypotensive period a significant decrease in CMRo$_2$ from 2.32 to 1.73 ml/100 g min^{-1} was observed, while CBF was unchanged. The change in CMRo$_2$ represents a 48% decrease compared with the awake state, and this finding accords with the decrease in CMRo$_2$ observed during isoflurane-induced hypotension to MAP 51 mm Hg using 2.3% isoflurane (Newman, Gelb and Lam, 1986). The decrease in CMRo$_2$ in association with an unchanged CBF obtained during the hypotensive period also is in accordance with the findings of Newman, Gelb and Lam (1986). These findings are associated with a decrease in ($Ca_{O_2} - Cv_{O_2}$) and an increase in oxygen saturation of jugular venous blood, indirectly indicating an increase in oxygen tension of cerebral tissue. Animal studies on isoflurane-induced hypotension support these findings (Seyde and Longnecker, 1986).

Previous studies, and that presented here, suggest that isoflurane-induced hypotension induces a significant decrease in CMRo$_2$, while CBF is unaffected. Experimental studies suggest that the decrease in CMRo$_2$ might protect the brain against ischaemia. These observations, together with studies of cerebral autoregulation showing partially intact autoregulation during isoflurane anaesthesia (Todd and Drummond, 1984), and studies in dogs (Artru, 1986) indicating partial preservation of carbon dioxide reactivity, suggest that isoflurane has a place during surgery for intracranial space-occupying lesions, and that isoflurane might be an alternative to sodium nitroprusside and other drugs during craniotomy for surgery on cerebral aneurysm. However, during the acute stage of subarachnoid haemorrhage, impairment of cerebral autoregulation has been found (Kamiya, Kuyama and Symon, 1983; Voldby, Enevoldsen and Jensen, 1985b). Therefore, induced hypotension at this time may be dangerous and effects different to those found in

TABLE I. *Cerebral haemodynamic values (mean ± SEM) in 10 patients subjected to craniotomy for cerebral aneurysm during isoflurane-induced hypotension.* *$P < 0.05$ *compared with the prehypotensive values (paired t test)*

Cerebral haemodynamic values	Before hypotension	Hypotension	After hypotension
Mean inspired isoflurane concentration (%)	0.75	2.2 ± 0.2*	0.75
Mean arterial pressure (MAP) (mm Hg)	74.5 ± 2.2	54.6 ± 1.2*	77.2 ± 3.5
Pa$_{CO_2}$ (kPa)	4.1 ± 0.1	4.0 ± 0.2	4.1 ± 0.2
Central temperature (°C)	36.5 ± 0.1	36.0 ± 0.3*	35.6 ± 0.3*
Cerebral blood flow (CBF) (ml/100 g min^{-1})	34.3 ± 2.1	39.1 ± 5.0	40.7 ± 3.3*
Cerebral metabolic rate for oxygen (CMRo$_2$) (ml/100 g min^{-1})	2.32 ± 0.16	1.73 ± 0.16*	2.14 ± 0.24

this study (carried out after the 5th day), could be anticipated.

In the posthypotensive period a significant increase in CBF — as compared with the prehypotensive period — was observed. This increase was not associated with changes in MAP or Pa_{CO_2}, suggesting that loss of autoregulation, or changes in cerebrovascular resistance, influenced these findings. This observation is in conflict with other studies in man in which posthypotensive hyperaemia was not observed (Newman, Gelb and Lam, 1986). However, studies in baboons suggest that a posthypotensive increase in CBF does occur (Van Aken et al., 1985), but the significance of this hyperaemia has not been studied. An explanation could be a direct effect of isoflurane, and that isoflurane was still present in the cerebral tissue at the time of the third CBF measurement. Studies in animals indicate that the desaturation of isoflurane in brain tissue is not completed for at least 20 min (Lam, Brown and Manninen, 1986).

The present study of isoflurane-induced hypotension supports a recent study of CBF and CMRo$_2$ indicating that CMRo$_2$ decreases and CBF is well maintained during the hypotensive period. These studies, together with animal studies, indicate that isoflurane may be preferred to halothane, nitroprusside and trimethapan. However, the evidence of moderate hyperaemia found in the postoperative period in the present study requires further evaluation.

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CEREBROVASCULAR EFFECTS OF ISOFLURANE IN MAN

Intracranial Pressure and Middle Cerebral Artery Flow Velocity

T. LUNDAR, K.-F. LINDEGAARD, L. REFSUM, R. RIAN
AND H. NORNES

SUMMARY

Twelve hydrocephalic patients undergoing hydrodynamic studies and shunt procedures during general anaesthesia were subjected to short term observations of the cerebrovascular effects of isoflurane. Intraventricular pressure (IVP), arterial pressure (AP); cerebral perfusion pressure (CPP = AP – IVP), end-tidal $P\text{CO}_2$, *Cerebral Function Monitor (CFM) activity and middle cerebral artery (MCA) flow velocity were measured. Introduction of 1% isoflurane for a 10-min period did not cause significant changes in IVP or MCA flow velocity, but caused marked and significant reductions in arterial pressure and CPP, and increases in CFM activity. In five patients 2% isoflurane was administered for another 5 min before discontinuation of the isoflurane. This caused further significant reduction in arterial pressure and increased IVP in four of the five patients. The decrease in CPP was thus even greater than the reduction in arterial pressure and the CFM activity decreased in four out of five patients. The MCA flow velocity did not change significantly.*

Although isoflurane appears to possess certain advantages over the older inhalation agents in the provision of anaesthesia for neurological surgery, a number of aspects require further clarification. The aim of the present study was to delineate the immediate effects of the administration of isoflurane on intracranial pressure and cerebral perfusion pressure, and on the basic mechanisms which regulate cerebral perfusion. In the intraoperative situation described, any rapid or untoward increase in the intracranial pressure could be easily counteracted by the drainage of ventricular fluid or by hyperventilation.

PATIENTS AND METHODS

Twelve hydrocephalic patients (eight female) scheduled for hydrodynamic studies and shunt procedures under general anaesthesia were included in the study. The series included patients with possible, or probable, occlusion of the aqueduct, in whom lumbar hydrodynamic studies would be misleading, or patients in whom lumbar cerebrospinal fluid (CSF) infusion tests had given inconclusive results.

The patients were aged between 13 and 71 yr (mean 44 yr). Their clinical symptoms and signs included headache, intellectual impairment, ataxia and incontinence of urine of varying degrees. CT scans had demonstrated marked ventricular, including 3rd ventricular, enlargement above the tentorium. There was no enlargement of the 4th ventricle. There were no clear periventricular lucencies or compression of the basal cisterns, and the sulci over the hemispheres were, at least partially, preserved. Thus there was no clear evidence of "pressure hydrocephalus" in any patient. On clinical and radiological grounds, the indication for a shunt procedure was judged to be uncertain in all patients. These patients were candidates for continuous recording of the intracranial ventricular pressure (IVP) for a period, including an intraventricular resorbtion test (Katzman and Hussey, 1970; Magnaes, 1978) with infusion of artificial CSF. General anaesthesia was used to reduce the number of ventricular punctures, to perform implantation of

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T. LUNDAR, M.D., K.-F. LINDEGAARD, M.D., H. NORNES, M.D. (Department of Neurosurgery); L. REFSUM, M.D., R. RIAN, M.D. (Department of Anaesthesiology); Rikshospitalet, University of Oslo, Oslo, Norway. Accepted for Publication: April 3, 1987.

a complete shunt system at the same time and to permit the maintenance of a constant $P\text{CO}_2$ during the test.

General anaesthesia was induced with a barbiturate and fentanyl and maintained with 70% nitrous oxide in oxygen. Alcuronium was administered to provide neuromuscular blockade. Arterial pressure (AP) and intraventricular pressure (IVP) were recorded using standard fluid-filled pressure transducers (AME, Horten, Norway), with zero reference at the midcranial level. Cerebral electrical activity was recorded using a cerebral function monitor (CFM) (CFM 4640, Devices Limited, Jersey, Great Britain). End-tidal $P\text{CO}_2$ was recorded (Sirecust System 400, Siemens, Erlangen, Federal Republic of Germany). Flow velocity in the left MCA was recorded continuously during the period of the study by transcranial Doppler (TCD). Doppler signals from the middle cerebral artery (MCA) were obtained using a laboratory prototype, range gated, 2-MHz, pulsed Doppler instrument with acoustically focusing transducer. The instrument and examination procedure have been described previously in detail (Aaslid, Markwalder and Nornes, 1982; Aaslid, Huber and Nornes, 1984; Lindegaard et al., 1985). All variables were recorded on a six-channel pen recorder (W+W Electronic AG, Basel, Switzerland) and on a seven-channel instrumentation tape recorder (Teac R 71, Teac, Tokyo, Japan).

After implantation of the ventricular cannula in the frontal horn of the right lateral ventricle, continuous recording of the IVP was established at steady-state to determine pre-test IVP before the hydrodynamic studies. The 1% isoflurane was administered for 10 min to all 12 patients. In six patients this was performed during hypocapnia ($P\text{CO}_2$ 3.9–4.4 kPa) and in six patients during normocapnia ($P\text{CO}_2$ 5.0–5.4 kPa). In five patients, in whom the decrease in arterial pressure was modest, and in whom there was no marked increase in IVP, 2% isoflurane was administered for a further 5 min.

The statistical significance of the changes induced by isoflurane was analysed by Wilcoxon's test for paired data. $P < 0.05$ was considered significant.

RESULTS

Mean arterial pressure was reduced following the introduction of 1% isoflurane to all 12 patients (APa to APb in figure 1): mean arterial pressure decreased from 88 to 70 mm Hg ($P < 0.001$, Wilcoxon's test for paired data). The intraventricular pressure was affected minimally by 1% isoflurane (IVPa to IVPb in figure 1) ($P > 0.05$). Cerebral perfusion pressure (CPP = AP − IVP) was reduced in all 12 patients, by between 3 and 38 mm Hg after the introduction of 1% isoflurane (fig. 1) ($P < 0.001$). The resulting CPP values were between 46 and 70 mm Hg. Only minor changes in the MCA flow velocity were observed following the introduction of 1% isoflurane (MCAa to MCAb in figure 1) ($P > 0.05$). The CFM activity increased at the same time in 11 of the 12 patients.

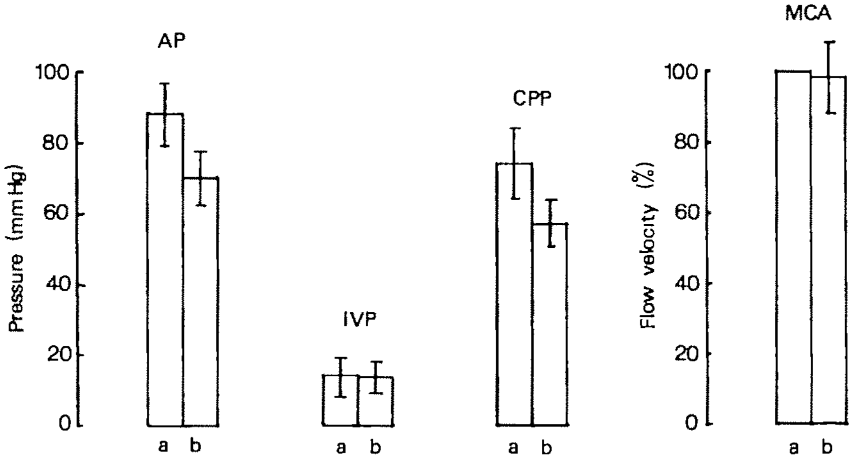

FIG. 1. Arterial pressure (AP), intraventricular pressure (IVP), cerebral perfusion pressure (CPP) and middle cerebral artery (MCA) flow velocities for the 12 patients before isoflurane (a) and 10 min after administration of 1% isoflurane (b). Mean values and SEM.

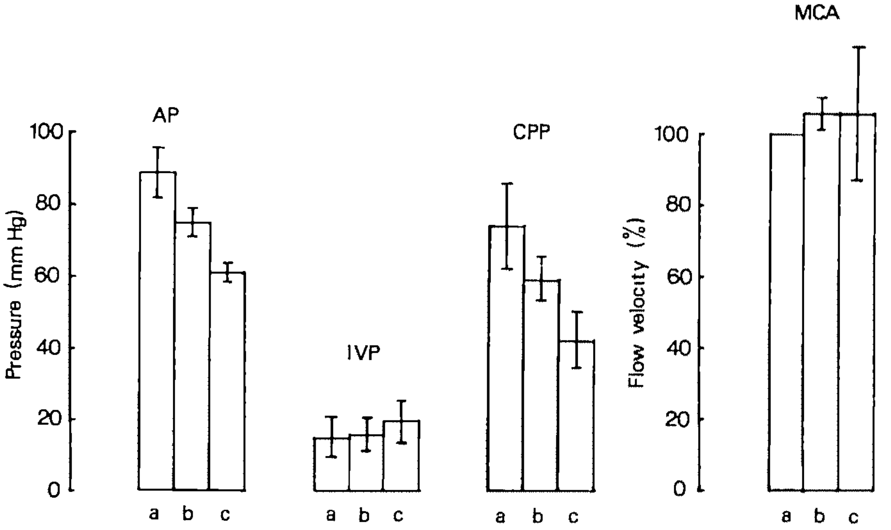

FIG. 2. Arterial pressure (AP), intraventricular pressure (IVP), cerebral perfusion pressure (CPP) and middle cerebral artery (MCA) flow velocities in patient 3, 4, 6, 9 and 11 before isoflurane (a), after 10 min of 1% isoflurane (b), followed by 5 min 2% isoflurane administration (c). Mean values and SEM.

In all the five patients to whom 2% isoflurane was administered for a further 5 min, arterial pressure was observed to decrease further (from 75 to 61 mm Hg (from APb to APc in figure 2)). In three patients there was an obvious increase in IVP of 4–8 mm Hg. As a result, CPP was further reduced by 10–26 mm Hg, and reached values of 28–48 mm Hg. The decreases in arterial pressure and CPP were significant ($P < 0.05$, Wilcoxon's test for paired data). The CFM record demonstrated decreased activity in four patients during the administration of the 2% isoflurane. During this period MCA flow velocity was increased in three patients and reduced in the other two. The three patients in whom flow velocity increased were the same three patients in whom the increase in IVP occurred. Figure 3 demonstrates the observed effects of 1% and 2% isoflurane in one of these patients.

Arterial pressure and IVP were similar in the hypocapnic and normocapnic groups before the introduction of 1% isoflurane.

After the discontinuation of the isoflurane, arterial pressure started to increase in about 20 s (fig. 3) and the observed effects on IVP, MCA flow velocity and CFM were reversed within 5–10 min. Increases in heart rate were observed in some patients as arterial pressure was decreased, but no electrocardiographic abnormalities were seen. Isoflurane seemed to be well tolerated.

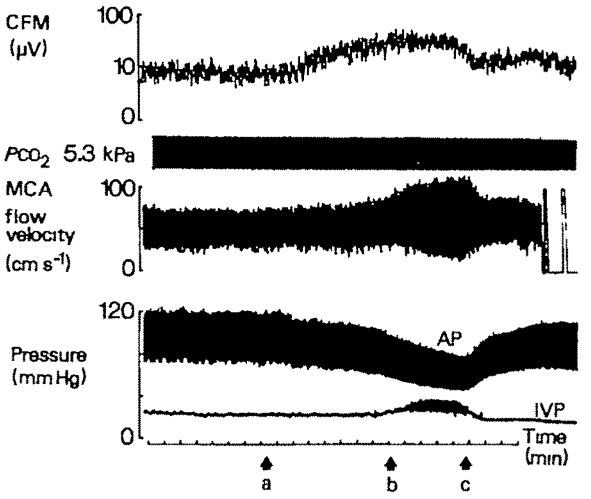

FIG. 3. Simultaneous records of CFM activity, end-tidal P_{CO_2}, MCA flow velocity, AP and IVP in patient 9. At arrow **a**, 1% isoflurane was administered. Arterial pressure was reduced from 88 to 76 mm Hg, while IVP remained unchanged (22 mm Hg), thereby reducing CPP (AP – IVP) by 12 mm Hg to 54 mm Hg. MCA flow velocity increased moderately from 45 to 50 cm s^{-1} during the same period, while the CFM activity was increased. At arrow **b**, the isoflurane administration was increased to 2%. A further reduction in AP from 76 to 58 mm Hg was accompanied by increased IVP from 22 to 30 mm Hg, reducing CPP by further 26 mm Hg, to 28 mm Hg; MCA flow velocity increased concomitantly from 50 to 55 cm s^{-1} and the CFM activity decreased. As isoflurane was discontinued, arrow **c**, all observed changes were rapidly reversed.

DISCUSSION

The short term use of isoflurane in this setting may imply that steady-state isoflurane anaesthesia was never reached in these patients. From a neurosurgical point of view it is, however, the acute effects of isoflurane on intracranial pressure, cerebral perfusion pressure and on the cerebral perfusion itself that are most relevant. The administration of 1% isoflurane caused an obvious decrease in arterial pressure in all patients. This is a well known effect and is the basis for the use of isoflurane as an easily controllable hypotensive agent in cerebral aneurysm surgery (Lam and Gelb, 1983).

In these hydrocephalic patients, slight decreases in IVP were seen as often as slight increases during the administration of 1% isoflurane in the hypocapnic and the normocapnic groups. Consequently, there was no overall significant change in IVP at this point in the study. The introduction of 1% isoflurane caused a marked decrease in cerebral perfusion pressure. With 2% isoflurane, IVP increased in four of the five patients. Combined with the further reductions in arterial pressure, this resulted in marked reductions in CPP. The observed changes in intracranial pressure after the introduction of isoflurane are in accord with previous clinical studies performed in patients with supratentorial mass lesions (Adams et al., 1981; Campkin, 1984).

Radioactive tracer techniques, although well established for use during steady state, are too slow to study dynamic changes in cerebral blood flow. Moreover, in the clinical situation, they can provide only a limited number of values as a result of the use of ionizing radiation. The transcranial Doppler ultrasound technique permits atraumatic recordings of blood flow velocity in defined basal cerebral arteries (Aaslid, Markwalder and Nornes, 1982). Recent clinical work has shown that this method provides clinically important information on individual haemodynamic conditions in patients with subarachnoid haemorrhage, precerebral artery disease, intracranial artery stenosis and cerebral arteriovenous malformations (Aaslid, Huber and Nornes, 1984; Lindegaard et al., 1985; Lindegaard, Bakke et al., 1986; Lindegaard, Grolimund et al., 1986).

The middle cerebral artery carries about 80% of the flow volume received by the cerebral hemisphere (Toole, 1984). Changes in MCA flow should, therefore, be fairly representative of changes in brain perfusion as a whole. We have previously reported our experiences with continuous monitoring of MCA flow velocity during open-heart surgery (Lundar et al., 1985a, b; Lundar et al., 1986). Comparative studies in a few of these patients demonstrated that individual changes in MCA flow velocity reflected concomitant changes in ipsilateral (electromagnetically recorded) internal carotid artery volume flow.

Flow volume through a given vessel segment equals flow velocity multiplied by the area of the vessel lumen. Probably reflecting the well known individual differences in the diameter of the proximal MCA as well as individual variation in baseline cerebral blood flow, the normal MCA flow velocity is from about 35 to 90 cm s^{-1}, with a mean about 60 cm s^{-1} under resting conditions (Aaslid, Markwalder and Nornes, 1982; Lindegaard et al., 1985). Individual differences thus preclude comparisons of absolute MCA flow velocity in a series of individuals. Using relative terms, however, MCA flow velocity shows reactivity to carbon dioxide (per cent flow velocity change per unit of change in $P\text{CO}_2$) of about $25.5 \pm 6.0\%$ kPa^{-1} ($3.4 \pm 0.8\%$/mm Hg) (Markwalder et al., 1984). This is in accordance with the $30.8 \pm 7.5\%$ kPa^{-1} ($4.1 \pm 1\%$/mm Hg) carbon dioxide reactivity of cerebral blood flow determined by means of the xenon washout technique (Olesen, Paulson and Lassen, 1971). Together, these data indicate that the diameter of the proximal MCA remains near constant under physiological conditions. Recently, a comparative study between MCA flow velocity and xenon technique confirmed that individual changes in MCA flow velocity reflect concomitant changes in cerebral blood flow (Bishop et al., 1986).

The MCA flow velocity was not changed by the introduction of 1% isoflurane, in spite of the considerable reduction in perfusion pressure. During 2% isoflurane administration, three patients demonstrated increased MCA velocity, while two patients showed some reduction. In the face of the decreases in CPP to values in the range 28–48 mm Hg, this is remarkable. Being a potent vasodilator, isoflurane might distort the flow–velocity relation in the proximal MCA that appears to remain relatively constant in many other situations. A number of previous studies have demonstrated unchanged brain perfusion during anaesthesia with 1% isoflurane, using xenon, venous outflow or microsphere techniques.

At higher isoflurane concentrations, brain perfusion was found unchanged or even enhanced (Cucchiara, Theye and Michenfelder, 1974; Newberg, Milde and Michenfelder, 1983; Gelman, Fowler and Smith, 1984; Todd and Drummond, 1984). From this knowledge, it appears unlikely that the preserved or even increased MCA flow velocity values observed in the present study were caused by a constriction of the proximal MCA segment. If the diameter of the proximal MCA is changed, it seems most likely that there is a slight dilatation during increasing isoflurane concentrations. We assume, therefore that the changes in MCA flow velocity during isoflurane anaesthesia reflect changes in brain perfusion with an accuracy that is clinically useful.

The observed changes in CFM activity during administration of 1% and 2% isoflurane in the present study are in accord with previous reports (Pauca and Dripps, 1973; Newberg, Milde and Michenfelder, 1983) and indicate that the depth of isoflurane anasethesia can be followed on the CFM record.

The influence of isoflurane on cerebral autoregulation cannot be assessed from the present study. Our observations during 1% isoflurane with almost constant MCA flow velocity during CPP reductions of up to 38 mm Hg, down to values of 50 mm Hg, would be compatible with well preserved autoregulation. When, however, cerebral perfusion seems to be increased during 2% isoflurane, a direct effect on the cerebral vasculature which is more pronounced than the effect on the systemic circulation, must be considered.

Isoflurane has been shown to reduce the resistance to reabsorption of cerebrospinal fluid in dogs (Artu, 1984). This effect may be of particular value in hydrocephalic patients, in whom the impaired reabsorption of CSF contributes to reduced intracranial compliance.

During the administration of 2% isoflurane, the combination of the decreases in arterial pressure and the increases in IVP produced CPP values in the range 28–48 mm Hg. To increase IVP at such values of arterial pressure and CPP would be considered unwanted and potentially dangerous. The recording demonstrated, however, that flow velocity increased as the IVP increased. These increases in IVP did not appear to indicate a threat to the cerebral perfusion, but rather to be a consequence of the remarkably well preserved cerebral circulation at these low values of CPP. It should be understood clearly that these observations were obtained in hydrocephalic patients. The results should not be extrapolated to other patients such as those with head injury, stroke or subarachnoid haemorrhage. Further studies are needed to delineate the cerebral effects of isoflurane in such conditions.

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SINGLE BREATH INDUCTION OF ANAESTHESIA WITH ISOFLURANE

J. M. LAMBERTY AND I. H. WILSON

SUMMARY

This study has compared a single breath induction technique and a conventional inhalation induction technique using isoflurane in nitrous oxide and oxygen. Each group consisted of 36 unpremedicated patients. Single breath induction was associated with fewer problems on induction, but required more patient co-operation. Ninety-four percent of patients were willing to repeat the single breath induction technique, compared with 74% of patients receiving a conventional inhalation induction.

Two studies have demonstrated that the induction of anaesthesia using a single breath of either halothane and oxygen alone (Ruffle et al., 1985) or halothane, nitrous oxide and oxygen (Wilton and Thomas, 1986) is effective, safe and acceptable to patients. However, as concern has been expressed recently over the dangers associated with repeated halothane anaesthesia (Editorial, 1986a), we have assessed the suitability of isoflurane for use as an alternative to halothane in a single breath induction technique.

PATIENTS AND METHODS

Seventy-two patients (ASA grade I or II) aged between 11 and 65 yr, who consented to an inhalation induction of anaesthesia, were divided randomly into a control group and single breath induction group. The patients were scheduled to undergo minor outpatient surgery under general anaesthesia.

In the control group anaesthesia was induced via a Mapleson A breathing system, using an initial mixture of 0.5% isoflurane with 66% nitrous oxide in oxygen. A fresh gas flow of approximately 100 ml kg^{-1} was delivered through a calibrated vaporizer (Mark 3 Fluotec). The isoflurane was increased by 0.5% after every fifth breath, unless some complication, such as coughing, warranted a modification of the technique. The maximum concentration of isoflurane was 4%.

The single breath induction group inhaled a vital capacity breath of 2% isoflurane with 66% nitrous oxide in oxygen. This was administered from a modified Mapleson A breathing system to which an extra 2-litre reservoir bag had been added (fig. 1). The choice of 2% isoflurane was initially empirical but, having been found to be satisfactory, was used throughout the study.

The technique was explained to the patient who was then given a mask with a right-angled connector attached. After becoming familiar with breathing through the mask, the patient was asked to exhale fully whilst the breathing system was attached to the right-angled connector by the

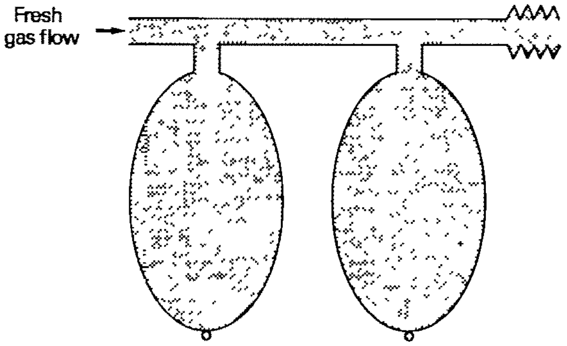

FIG. 1. Modified Mapleson A breathing system.

J. M. LAMBERTY,* M.B. B.S., F.F.A.R.C.S.; I. H. WILSON, M.B. CH.B., F.F.A.R.C.S; Department of Anaesthesia, Freedom Fields Hospital, Plymouth PL4 8QQ. Accepted for Publication: May 7, 1987.

*Present address, for correspondence: The Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW.

anaesthetist. A fresh gas flow of not less than 8 litre min^{-1} and light thumb occlusion of the outlet of the breathing system were maintained to ensure both 2-litre bags were full, but not under tension. The patient was instructed to inhale fully and to hold the breath for as long as was comfortable. Following loss of consciousness, and after the development of regular breathing, the concentration of isoflurane was increased by 0.5% every fifth breath to a maximum of 4%.

Monitoring in both groups was identical: arterial pressure (Dinamap 845XT Critikon) and the ECG were recorded before induction, and then at 60-s intervals for 5 min after the loss of consciousness.

We assessed an induction as complicated if one or more problems occurred. All problems could be categorized into one of the five groups shown in table II. As it is difficult to assess such observations objectively, we were very strict in our definition. We included a single cough, or movement of a limb; excessive salivation was recorded when our hands became wet. Usually the sequence of events was unequivocal, with excess salivation including coughing and breath-holding.

We categorized patients' performance of the manoeuvres requested of them as good, moderate or poor. Good performance implied full compliance with the technique. Moderate performance was recorded when the patient did not fully comply with the instructions, for example by not taking a full vital capacity breath after maximum expiration but when induction was achieved satisfactorily. Poor performance was recorded when the patient was unable to complete the manoeuvres requested. Finally, when seen after operation, the patients were asked how they would describe the induction procedure, whether they would be willing to undergo a similar induction technique again, and how many breaths they remembered taking. Statistical analyses were carried out using the chi-square test, Fisher's exact test, and the Mann–Whitney *U* test, as appropriate.

RESULTS

Anaesthesia was successfully induced by the selected technique in 35 patients in each group; one induction in each group had to be abandoned.

TABLE I. *Demographic data of patients*

	Males	Females	Age (yr) Median (mean)	Age (yr) Range
Control group ($n = 36$)	19	17	36 (36.3)	11–65
Single breath group ($n = 36$)	21	15	32 (34.2)	12–64

TABLE II. *Incidence of complications during induction of anaesthesia.* **$P < 0.01$

	Control group ($n = 36$)	Single breath group ($n = 36$)
Induction		
Complicated	18 (50%)	7 (19%)**
Uncomplicated	18 (50%)	29 (81%)
Coughing	8 (22%)	5 (14%)
Laryngospasm	8 (8%)	1 (3%)
Breath holding	9 (25%)	3 (9%)
Movements	11 (30%)	5 (14%)
Secretions	8 (22%)	3 (9%)
Abandoned	1	1

The demographic data of the two groups are shown in table I. The most common complications of any inhalation technique are compared between the two groups in table II. There were less complicated inductions in the single breath group. The most troublesome complications, coughing, laryngospasm and excessive salivation were also less common in the single breath induction group.

Cardiovascular stability and the incidence and types of arrhythmia were similar in both groups (table III).

Patients' performance of the single breath technique was inferior to the conventional inhalation technique. Conversely, patients preferred the single breath technique, and more of the patients in the single breath group indicated that they would be willing to have that induction technique repeated. When asked how many breaths they remembered taking before loss of consciousness, patients in the single breath group remembered taking significantly fewer breaths (table IV).

DISCUSSION

Two studies have determined the safety and acceptability of using a single vital capacity breath of halothane in oxygen for the rapid induction of anaesthesia (Ruffle, Latta and Snider, 1982;

TABLE III. *Comparison of cardiovascular stability between techniques. Mean values (SD). †Excludes abandoned inductions*

	Before induction	After induction (min)				
		1	2	3	4	5
Control group ($n = 35$†)						
Systolic pressure	139	134	132	135	135	132
(mm Hg)	(23)	(22)	(23)	(26)	(23)	(24)
Diastolic pressure	92	88	86	90	85	83
(mm Hg)	(19)	(22)	(22)	(22)	(22)	(22)
Heart rate	86	90	93	86	84	82
(beat min^{-1})	(14)	(12)	(14)	(14)	(13)	(14)
Arrhythmias	0	Atrial ectopic			1	
		Nodal rhythm			1	
		Ventricular ectopics			3	
Single breath group ($n = 35$†)						
Systolic pressure	136	132	131	29	127	126
(mm Hg)	(16)	(20)	(19)	(21)	(18)	(19)
Diastolic pressure	90	87	86	85	85	84
(mm Hg)	(11)	(16)	(14)	(14)	(12)	(14)
Heart rate	82	88	92	90	84	80
(beat min^{-1})	(12)	(14)	(13)	(12)	(12)	(13)
Arrhythmias	0	Atrial ectopic			1	
		Nodal rhythm			1	
		Ventricular ectopics			2	

TABLE IV. *Patient co-operation and acceptability. †Excludes abandoned inductions.* $*P < 0.05$; $***P < 0.001$

	Control group ($n = 36$)	Single breath group ($n = 36$)
Co-operation		
Good	31 (86%)	27 (77%)
Fair	4 (11%)	5 (14%)
Poor	1 (3%)	3 (9%)
Same induction again?		
†Yes	26 (74%)	33 (94%)*
No	9 (26%)	2 (6%)
Breaths remembered (median)*	5	2***

Ruffle et al., 1985). These studies used healthy volunteers, and the authors used the technique successfully in more than 200 patients. In 1986 Wilton and Thomas modified the technique by using halothane in nitrous oxide and oxygen. Their study of 100 patients again attested to the acceptability of the technique for the rapid induction of anaesthesia.

The use of a single vital capacity breath technique for the rapid induction of and recovery from anaesthesia is particularly attractive for minor day-case, and accident and emergency, surgery. These patients will usually be unpremedicated and, therefore, at their most co-operative. The lack of premedication and the avoidance of an i.v. induction agent, should assure that the patient has the best chance of being alert in the postoperative period.

The conclusions of a symposium on halothane and the liver have been reported (Blogg, 1986; Editorial, 1986a), and policy outlined by the Committee on Safety of Medicines (1986). Another editorial in the *Lancet* (Editorial, 1986b) acknowledged the advantages of a single breath technique, and emphasized again the problems associated with repeated halothane anaesthesia.

We have assessed the suitability of isoflurane using the recently described single breath induction technique. We chose isoflurane rather than enflurane because a pilot study indicated that

TABLE V. *Vapour characteristics*

	Isoflurane	Enflurane	Halothane
Molecular weight	184.5	184.5	197.4
MAC in oxygen	1.28	1.58	0.75
Partition coefficients (37)			
Blood–gas	1.4	1.9	2.3
Oil–gas	97.8	98.5	224
Percentage biotransformed	0.2 %	2.4 %	25 %

isoflurane was, surprisingly, acceptable to patients. Our clinical impression was that isoflurane would have been less acceptable because of its pungent odour, as in the case with conventional inhalation induction techniques (Pandit, Steude and Leach, 1985). Pandit and colleagues have, however, suggested that isoflurane may become more acceptable for outpatient anaesthesia with the introduction of different techniques of induction.

When the physical characteristics of the three vapours are compared, it is apparent that isoflurane should have a more rapid induction and emergence, and be less accumulative than the other two (table V). Isoflurane has a low percentage of biotransformation (0.2 %) and it has been suggested that the problems of pollution could be less than with the other vapours (Blogg, 1986). Therefore, not only could isoflurane become a useful alternative to halothane when repeat anaesthesia is contemplated, it could also become the agent of choice for day-case surgery. However, when multibreath induction of anaesthesia with isoflurane has been used in outpatient anaesthesia, it has been found to be less satisfactory than halothane (Pandit, Steude and Leach, 1985).

Our study with isoflurane compared the two techniques of inhalation anaesthetic induction for complications and acceptability to patients. In our control group the findings confirm previous studies that isoflurane causes excitatory movements and an excessive amount of salivation, and that, although safe, it is less acceptable to both patient and anaesthetist than is halothane. This upper airway irritability (Jones, 1985) has been attributed to the etheral odour of isoflurane (Editorial, 1986b).

In our single vital capacity breath group the complications were all less frequent than with a conventional induction (tables II, IV). The patients found the technique to be more acceptable, and 94 % of them would have accepted the technique again. Although there was a greater incidence of moderate and poor compliance with the single breath technique in our study, than found by Wilton and Thomas, this did not reach statistical significance. The median number of breaths remembered by the single breath group was two, compared with five in the control group (table IV).

The superiority of the single breath technique with isoflurane is surprising (Editorial, 1986b), but may be explained by the low blood–gas solubility coefficient, causing the onset of anaesthesia to be relatively fast. The patient may pass through the conventional stages of light anaesthesia in much the same manner as occurs with i.v. induction agents. We believe that, with this technique of induction, isoflurane can be used more successfully for gaseous induction of anaesthesia. However, it should be noted that isoflurane is not superior to halothane for smoothness of induction, and had a higher complication rate when compared with the results of Wilton and Thomas. However, it is a reasonable alternative for the many situations in which halothane may be undesirable. The editorial in the *Lancet* (Editorial, 1986b), suggested that the physical characteristics of isoflurane would lead to a prolonged and unsatisfactory single breath induction. Our study suggests that this is not so, and that a single breath induction with isoflurane is a practical alternative to halothane.

In each group there was one patient in whom coughing and salivation were such that the technique had to be abandoned. In both patients the trachea was intubated subsequently to facilitate control of the airway. It was noted that both of these patients were smokers, and it is our clinical impression that possible difficulties on induction should be anticipated where there is coexistent upper airway irritability, whether from a recent upper respiratory tract infection or smoking, and that in these patients the single breath induction with isoflurane should not be attempted.

In conclusion, we believe that isoflurane is a useful alternative to halothane for use in a single vital capacity breath induction, when the latter agent is unsuitable. The use of isoflurane in day-case and casualty surgery is attractive and, when inhalation induction is planned, single breath induction is more acceptable to the patient.

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ISOFLURANE IN A CIRCLE SYSTEM WITH LOW GAS FLOW

S. P. REVELL AND D. H. TAYLER

SUMMARY

Isoflurane was administered from a Goldman vaporizer to a circle breathing system with low fresh gas flows. The uptake and vapour concentration of isoflurane were compared in two groups of spontaneously breathing patients receiving oxygen alone (n = 19), or nitrous oxide and oxygen (n = 30). Anaesthesia was maintained successfully in all patients. The authors believe this to be a safe and economical way of delivering isoflurane.

Isoflurane is not broken down by sunlight or soda-lime; thus it is suitable for use in low flow circle systems. Moreover, less than 0.2% of the administered dose of isoflurane can be recovered as urinary metabolites—compared with 2.5% of enflurane and 20% of halothane (Mazze, 1984). This minimal biodegradation may result in less nephrotoxicity and hepatotoxicity.

The cost of isoflurane is a disadvantage: at present, it is almost eight times as expensive as halothane by volume. The Goldman vaporizer has been used frequently in closed and low flow systems (Barton and Nunn, 1975; Robins, 1983). The aim of this study was to investigate the safety and efficacy of isoflurane when administered from a Goldman vaporizer into a low flow circle system.

PATIENTS AND METHODS

Forty-nine patients (ASA grades I or II) aged 18–70 yr took part in the study. They were undergoing orthopaedic, oral, plastic or general surgery likely to take 30 min or longer, in a general hospital. The local Ethics Advisory Committee approved the study and informed consent was obtained from each patient.

All patients were premedicated with an opioid (papaveretum or pethidine) and either hyoscine or atropine approximately 1 h before the induction of anaesthesia.

Anaesthesia was induced with sufficient thiopentone to obtund the eyelash reflex. This was followed by suxamethonium 1 mg kg^{-1} to facilitate tracheal intubation. The larynx was sprayed with 10% lignocaine, unless contraindicated, and either a cuffed oral tube or a cuffed nasal tube inserted.

The tracheal tube was connected to the anaesthetic system shown in figure 1. A standard Boyle's machine (British Oxygen Company) and circle system were used. Isoflurane vapour was generated by a vaporizer-in-circuit (VIC). A Goldman vaporizer was chosen because it has a low resistance to gas flow. The oxygen analyser was an Analytical Instruments Teledyne fuel cell. The vapour analyser was a Datex Normac, which uses the principle of infra-red absorption spectrophotometry (Luff and White, 1985). Our analyser had a mean sampling rate of

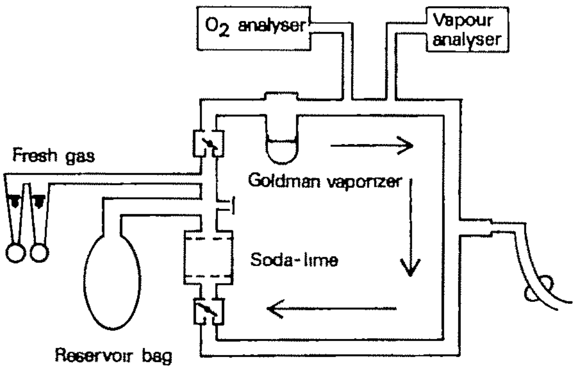

FIG. 1. Breathing system, showing location of analysers.

S. P. REVELL, M.B., CH.B.; D. H. TAYLER, M.B., B.S.; Department of Anaesthetics, Queen Mary's Hospital, Roehampton Lane, London SW15. Accepted for Publication: January 21, 1987.

Present address: Magill Department of Anaesthetics, Westminster Hospital, Horseferry Road, London SW1.

181 ml min^{-1}. The system was flushed with oxygen at 1 litre min^{-1} for a minimum of 5 min before use, to reduce the concentrations of previous vapours. The glass bowl of the Goldman vaporizer was filled with 30 ml of isoflurane liquid, using a glass syringe to measure the volume accurately.

The patient's lungs were ventilated manually during the period of apnoea following the administration of suxamethonium. A fresh gas flow of 3 litre min^{-1} was used with the vaporizer set at either the second or the fully-on notch. The 3-litre fresh gas flow was found to fill the reservoir bag rapidly and permit manual ventilation. The fresh gas flow was reduced to 500 ml min^{-1} when spontaneous ventilation returned. The vaporizer was adjusted to maintain a steady state of anaesthesia with appropriate isoflurane concentrations.

Oxygen alone was the fresh gas supplied to the first 19 patients (group A). In order to decrease the use of isoflurane further, nitrous oxide was incorporated to the inspired gas mixture in a second group of patients (group B). There were 30 patients in group B whose lungs were ventilated initially with nitrous oxide 2 litre min^{-1} and oxygen 1 litre min^{-1}. Fresh gas flows were reduced to oxygen 300 ml min^{-1} and nitrous oxide 200 ml min^{-1} (Virtue, 1974) when spontaneous breathing restarted. The electrocardiograph, and oxygen and vapour concentrations were monitored continuously for the duration of anaesthesia. The heart rate and arterial pressure were measured every 5 min. On completion of surgery, the vaporizer was switched off, the trachea was extubated and the patients were taken to the recovery room where they breathed oxygen-enriched air until awake.

The results were analysed by the Student's *t* test.

RESULTS

In table I, the mean ages, durations of anaesthesia and volumes of isoflurane used in the two groups of patients are compared. There were no significant differences in the age and duration of anaesthesia in groups A and B. However, isoflurane usage was significantly greater in group A ($P < 0.001$).

The mean concentrations of isoflurane delivered to the patients at each setting of the Goldman vaporizer—taken at 15-min intervals—are shown in table II. The vapour concentration settled rapidly after changes in vaporizer setting. The

TABLE I. *Comparison between patient groups A and B (mean values, SD)*

	Group A	Group B
Age (yr)	36.9 (15.5)	36.4 (18.4)
Duration of anaesthesia (min)	59.7 (23.8)	51.7 (24.0)
Isoflurane usage (ml h^{-1})	10.6 (3.4)	7.4 (1.7)

TABLE II. *Inspired isoflurane concentration (mean, SD) at each Goldman vaporizer setting*

Setting on Goldman vaporizer	Isoflurane concn (%)	
	Group A	Group B
1	1.15 (0.18)	1.09 (0.20)
2	3.43 (0.49)	3.54 (0.37)
Fully-on	4.57 (0.37)	—

TABLE III. *Nitrogen concentrations (mean, SD) (group A only) calculated for measurements taken at 30-min intervals*

Time after connection to breathing system (min)	Nitrogen concn (%)
30	16.2 (6.8)
60	9.7 (4.6)
> 60 (30-min intervals)	8.0 (2.3)

TABLE IV. *Mean inspired oxygen concentration (SD) from measurements taken at 30-min intervals*

Time after connection to breathing system (min)	Oxygen concentration (%)	
	Group A	Group B
30	81.9 (5.8)	45.4 (6.7)
> 30	90.0 (3.5)	42.6 (4.2)

TABLE V. *Price of anaesthetic agents for Riverside Health Authority*

Agent	Cost (£)	Cost per ml (£)	Hourly cost for agent at 1.5% in a Magill circuit with FGF 7 litre min^{-1} (£)
Isoflurane	17.00/100 ml	0.170	5.97
Halothane	5.75/250 ml	0.023	0.67
Soda-lime (4.5 kg)	5.84		

differences between these two groups were found to be non-significant. Carrier gas can affect vaporizer output, as has been demonstrated previously (Stoelting, 1971; Diaz, 1976).

Nitrogen concentration in the system was calculated for patients in group A at 30-min intervals using the formula:

$$\text{Nitrogen} = 100 - (\%\ \text{oxygen} + \%\ \text{isoflurane})$$

The results are shown in table III. Nitrogen concentrations decreased gradually after 30 min as a result of sampling by the Normac vapour analyser and loss through the expiratory valve.

Inspired oxygen concentrations at 30 min and after 30 min are shown in table IV. Oxygen concentrations at 30 min did not differ significantly from those observed after 30 min in group B.

Effect on cardiovascular system

The heart rate and arterial pressure tended to decrease in both groups; however, no treatment was required. An arrhythmia was noted in one patient having orthopaedic surgery, but it was present before surgery also. None of the nine patients undergoing extraction of wisdom teeth had arrhythmias.

Recovery

Recovery was rapid. All of the patients were conscious and able to return to their wards within 30 min of completion of anaesthesia. No difference in recovery time was noted between groups A and B.

DISCUSSION

The Goldman vaporizer has been evaluated previously as a draw-over vaporizer for halothane and enflurane in closed breathing systems (Mushin and Galloon, 1960; Barton and Nunn, 1975; Bushman et al., 1977; Jordan and Bushman, 1981; Robins, 1983). In this study, isoflurane was used in a similar breathing system in 49 patients. Nitrous oxide was used to decrease the amount of isoflurane needed to maintain anaesthesia in group B. As a result, the oxygen flow was reduced to 300 ml min^{-1}. This value approaches the basal consumption of 200 ml for an average adult, making it essential to monitor the inspired oxygen concentration.

In this study the nitrogen concentration decreased below expected values as a result of sampling by the Normac vapour analyser and loss through the expiratory valve.

The vapour concentrations for each setting on the Goldman vaporizer were not significantly different in the two groups. The Datex Normac infra-red vapour analyser is not affected by nitrous oxide or nitrogen and so gives similar values for the two groups. The volume of isoflurane used per hour was significantly greater in group A. Each 10% of nitrous oxide is known to reduce the required minimal alveolar concentration of an anaesthetic vapour by 10% (Eger, 1981). As there was no significant difference in the mean duration of anaesthesia between the two groups, the increased usage in group A was attributed to the higher vaporizer settings required to maintain anaesthesia in that group.

The advantages of low flow re-breathing systems include increased humidification and reduced heat loss (Edsall, 1981). The risk of atmospheric pollution is decreased: it has been shown previously that the halothane concentration in the operating theatre was 500 times lower when a closed, rather than a semi-closed, system was used (Barton and Nunn, 1975).

Isoflurane is almost eight times more expensive by volume than halothane in this hospital (Q.M.H.) (table V). When used in a low flow breathing system, with nitrous oxide, it is still about twice as expensive as using 1.5% halothane in a Magill breathing system with a fresh gas flow of 7 litre min^{-1}. It is almost five times cheaper to use this closed system with nitrous oxide than to use isoflurane at 1.5% in a Magill breathing system at 7 litre min^{-1} fresh gas flow.

The use of soda-lime and the use of additional monitoring are extra expenses in low flow systems. The approximate hourly cost of soda-lime can be calculated. In a 70-kg man using closed systems, the 1.13-kg cannisters of soda-lime last about 4 h (Edsall, 1981). In this hospital, the cost would be about 35p per hour. The cost of monitoring depends upon the initial price and the maintenance of the equipment. The Datex Normac cost £1,780, plus VAT. Two cannisters of calibration gas are used monthly, at £5.40 each. Servicing is performed by our departmental technician. The oxygen analyser could be justified for use in conventional or low flow systems. Isoflurane in a low flow circuit when compared with the conventional type (table V) would have to be used for about 430 h before it becomes more economical.

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INFLUENCE OF VARIATIONS IN BLOOD HAEMOGLOBIN CONCENTRATION ON THE CALCULATION OF BLOOD LOSS AND VOLUMETRIC IRRIGATING FLUID BALANCE DURING TRANSURETHRAL RESECTION OF THE PROSTATE

R. G. HAHN

SUMMARY

Blood loss in 38 patients undergoing transurethral resection of the prostate (TURP) was calculated in four different ways by using various reference blood haemoglobin determinations (B-Hb) during the course of preparation and surgery. Blood loss became greater the later the B-Hb was drawn. This increase was because variations in B-Hb acted to underestimate the loss of plasma. The variations also distorted the irrigating fluid balance to give too low values for the absorption of irrigating fluid. It is possible to correct for the errors in blood loss and volumetric fluid balance by the use of haemodilution factors. Haemodilution was greater in patients with complications such as absorption of irrigating fluid or excessive blood loss than in patients without such features if Ringer's acetate was used for i.v. fluid supplementation. With dextran 40, all patients had a similar degree of haemodilution.

In many hospitals it is customary to measure volumetrically the irrigating fluid balance during transurethral resections of the prostate (TURP) since absorption of the irrigating fluid may be harmful (Hagstrom, 1955; Taylor et al., 1958). The balance is obtained as the difference between the input and the amount of irrigating fluid recovered. When less fluid is collected than given, the missing volume is considered to have been absorbed by the body.

Ideally, the amount of blood in the irrigating fluid recovered and the output of urine should be subtracted from the balance. There are several methods available to correct for the former source of error, which appears to be the more important.

The blood loss is usually calculated by measuring the haemoglobin content of the fluid recovered and dividing this figure by the blood haemoglobin concentration (B-Hb) (Desmond, 1973; Jansen, Berseus and Johansson, 1978). However, there is evidence to suggest that certain factors can interfere with this approach, such as variations in determination of blood haemoglobin concentration (B-Hb) during TURP. For this reason, it is necessary to take measurements throughout the procedure so as to estimate the actual blood loss.

This study was performed to investigate the influence of variations in B-Hb, before and during TURP, on the calculation of blood loss and irrigating fluid balance. The effect of using two different fluids for i.v. supplementation (Ringer's acetate solution or dextran 40) was also examined.

PATIENTS AND METHODS

Thirty-eight patients (mean age 70 yr, range 50–82 yr) scheduled for TURP because of benign prostatic enlargement were studied. All patients were given extradural anaesthesia via an indwelling extradural catheter, and received mepivacaine 9–14 ml with adrenaline (Carbocain-adrenalin, Astra, Sweden).

Irrigating fluid balance

The irrigating fluid was 2.2% glycine in water. The bags were weighed to the nearest gram before, and after, use and were suspended 60 cm above the patient's prostatic fossa. The intermittent bladder filling technique was used. A volumetric irrigating fluid balance was obtained every 10 min throughout each TURP by switching irrigating fluid bag and collection bucket. A sample for determination of the irrigating fluid haemoglobin

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Robert G. Hahn, M.D., Department of Anaesthesiology, Huddinge University Hospital, S-141 86 Huddinge, Sweden.
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concentration was taken from each collection bucket after manual stirring with a paddle for 30 s. If the irrigating fluid output, corrected for blood loss (see below), exceeded the input, the fluid balance was given a negative value; positive values indicated absorption.

Blood samples

These were drawn through an arterial cannula for determination of the blood haemoglobin concentration (B-Hb) and the serum sodium concentration (S-Na). Samples were taken: on the patient's admission to the hospital on the day before surgery (patient in the sitting position); before and after the induction of extradural anaesthesia; and every 10 min during the TURP at the time of bag and bucket change (recumbent position). The haemoglobin concentrations of the irrigating fluid and the blood samples were determined serially on a Coulter Counter S plus. Precision is specified by the manufacturer as 1 SD < 1.8 g litre^{-1} for the range measured. The accuracy of estimating blood loss from the haemoglobin concentration of the irrigating fluid was determined by dispersing known amounts of bank blood in irrigating fluid. It was found that the blood loss could be estimated within ± 5 ml. S-Na was determined by a flame photometer 543 (Instrumentation Laboratory) with a coefficient of variation of 0.55%.

Blood loss calculations

When calculating each 10-min blood loss, the haemoglobin concentration of the irrigating fluid was multiplied by its volume and divided by B-Hb. However, four different choices of reference B-Hb were used:

(1) The admission B-Hb was used throughout the TURP.

(2) The B-Hb obtained before induction of extradural anaesthesia.

(3) The B-Hb of blood drawn about 15 min after the anaesthesia had been established.

(4) The actual B-Hb measured at the time of each 10-min volumetric irrigating fluid balance.

The sum of the incremental blood losses was accepted as the total operative procedure blood loss (BL). Depending on the use of reference B-Hb, these were designated BL(1), BL(2), BL(3) and BL(4).

Comparisons between blood losses were made by calculating haemodilution factors; for instance BL(2)/BL(3), which then represents the haemodilution resulting from the extradural anaesthesia and the concomitant administration of i.v. fluid. BL(3)/BL(4) illustrates the influence of haemodilution during surgery on the calculation of blood loss.

I.v. fluid

Two regimens of i.v. fluid supplementation were used. In the first 28 patients, Ringer's acetate solution was given first in an amount of 10 ml kg^{-1} to prevent instability of arterial pressure during the induction of anaesthesia, and then at a rate of 50–150 ml every 10 min during the TURP. In the last 10 patients, 100–150 ml of dextran 40 (Rheomacrodex, Pharmacia, Sweden) was administered during the induction of anaesthesia and 25 ml every 10 min during the TURP.

Statistics

Mean values, standard deviation (SD), Student's paired and unpaired *t* tests as well as Friedman's two-way analysis of variance were used for statistics. When a skewed distribution of observations occurred, mean values and unpaired *t* test were replaced by median values and the Mann–Whitney test.

RESULTS

The blood losses BL(1)–(4) for all patients are shown in table I. Friedman's two-way analysis of variance showed a systematic difference between BL(1)–(4) both for Ringer's acetate solution and dextran. The calculated blood loss was greater the later B-Hb was drawn in nearly all patients so that BL(4) > (3) > (2) > (1).

The clinical course of each TURP was analysed and the patients were divided into three subgroups on the following criteria: (a) patients with a sum of positive 10-min irrigating fluid balances > 300 ml occurring together with a decrease in S-Na > 2 mmol litre^{-1} ($P < 0.005$), indicating intravascular absorption of irrigating fluid; (b) patients with BL(4) exceeding 700 ml; and (c) patients who did not fit any of these criteria.

Table II shows the haemodilution factors obtained by comparing the four different ways to estimate blood loss in all TURP patients as well as data of the subgroups. Since the subgroup classification was based on physiological events during the TURP, only subgroup haemodilution factors, including the intraoperative period, are

TABLE I. *Blood loss calculated in four different ways (BL(1)–(4)), in 28 patients receiving Ringer's acetate and 10 patients receiving dextran 40 for i.v. supplementation*

Ringer's acetate					Dextran 40				
	Blood loss (ml) with the use of					Blood loss (ml) with the use of			
Patient No.	BL(1)	BL(2)	BL(3)	BL(4)	Patient No.	BL(1)	BL(2)	BL(3)	BL(4)
1	519	591	630	676	1	927	1054	1113	1157
2	707	737	722	744	2	204	212	217	247
3	181	125	139	152	3	226	233	236	238
4	280	298	299	307	4	1089	1289	1211	1348
5	595	no value	670	708	5	158	175	181	195
6	245	254	259	260	6	284	284	397	418
7	215	236	242	269	7	491	531	552	571
8	948	1067	1153	1194	8	771	813	860	892
9	445	476	482	513	9	705	731	775	834
10	617	647	675	681	10	781	796	811	934
11	468	476	484	553					
12	148	148	157	159					
13	1034	1075	1153	1260					
14	429	443	471	478					
15	164	no value	180	180					
16	6	6	7	7					
17	1284	1325	1427	1530					
18	633	644	680	744					
19	95	107	118	119					
20	113	121	128	127					
21	66	69	75	93					
22	63	65	66	66					
23	251	277	298	299					
24	586	658	684	768					
25	462	502	494	507					
26	193	217	219	224					
27	192	203	219	224					
28	478	510	534	609					

TABLE II. *Haemodilution factors for all patients, representing preparation, induction of anaesthesia and surgery. Also shown is the classification of patients in clinical subgroups: (a) = intravascular absorption of irrigating fluid > 300 ml; (b) = blood loss > 70 ml; (c) = remaining patients. Some overlap occurred: in groups receiving Ringer's acetate and those receiving dextran, three patients were included in both group (a) and group (b)*

	Ringer's acetate ($n = 28$)			Dextran 40 ($n = 10$)		
BL(1)/BL(2) (mean ± SD)	0.94 ± 0.03			0.94 ± 0.04		
BL(2)/BL(3) (mean ± SD)	0.95 ± 0.03			0.94 ± 0.08		
BL(3)/BL(4) (mean ± SD)	0.95 ± 0.05			0.93 ± 0.04		
BL(1)/BL(4) (mean ± SD)	0.85 ± 0.06			0.83 ± 0.07		
	(a) ($n = 7$)	(b) ($n = 7$)	(c) ($n = 17$)	(a) ($n = 4$)	(b) ($n = 5$)	(c) ($n = 4$)
BL(3)/BL(4) (mean)	0.90	0.90	0.98	0.93	0.94	0.94
BL(1)/BL(4) (mean)	0.81	0.83	0.87	0.83	0.83	0.83
B-Hb change (median) (g litre^{-1})	−28	−22	−18	−31	−30	−30
S-Na change (median) (mmol litre^{-1})	−10	−1	−1	−7	−2	−2

TABLE III. *An irrigating fluid balance will show different values depending on which blood loss calculation is subtracted from the irrigating fluid recovered. The table illustrates the difference between using a single B-Hb blood loss calculation (BL(1)) and when using repeated determinations obtained during surgery (BL(4)). Also shown is the irrigating fluid balance when appropriate haemodilution factors are used to correct BL(1). *Patient No. 3 in the dextran group excluded because of incomplete information about irrigating fluid input*

			Irrigating fluid balance (ml) corrected for blood loss with		
	Patient No.	Sub-group	BL(1)	BL(4)	BL(1) and correction factor
Ringer's acetate	1	a	+316	+475	+430
	2	b	−98	−61	+57
	3	c	+649	+671	+667
	4	c	−130	−103	−89
	5	a, b	+355	+468	+485
	6	c	−37	−22	−1
	7	a	+40	+94	+87
	8	b	−252	−6	−44
	9	c	−377	−309	−311
	10	c	+1556	+1620	+1648
	11	a	+1697	+1782	+1799
	12	c	−249	−238	−226
	13	b	−615	−389	−388
	14	c	+334	+393	+408
	15	c	+79	+95	+103
	16	c	+14	+15	+15
	17	b	+196	+442	+477
	18	a, b	+1015	+1146	+1154
	19	c	−23	+1	−9
	20	c	−46	−32	−29
	21	c	−589	−562	−579
	22	c	−349	−346	−340
	23	c	−46	+2	−9
	24	a, b	+590	+772	+719
	25	c	−830	−785	−761
	26	c	−565	−534	−536
	27	c	−160	−128	−131
	28	a	+2685	+2816	+2790
Dextran 40	1	a, b	+490	+720	+680
	2	c	+211	+254	+253
	4*	b	−146	+113	+77
	5	c	−159	−122	−127
	6	c	−379	−245	−321
	7	c	+201	+281	+301
	8	b	−357	−236	−199
	9	a, b	+924	+1053	+1068
	10	a, b	+841	+994	+1001

shown in table II. Those are the BL(3)/BL(4) quotient, which represents haemodilution during surgery, and the BL(1)/BL(4) quotient, which includes haemodilution during preoperative preparation, induction of anaesthesia and surgery.

In patients who received Ringer's acetate, unpaired t tests showed that the BL(3)/BL(4) quotient in both subgroups (a) and (b) were different from (c) ($P < 0.001$). For the BL(1)/BL(4) quotient, there was a statistical difference between groups (a) and (c) ($P < 0.05$), while no difference was found between groups (b) and (c) ($P > 0.05$). In patients who received dextran, the subgroups showed similar haemodilution quotients (table II).

Since the irrigating fluid balance during a TURP is to be corrected for blood loss, the figure for irrigating fluid absorption will be influenced by which blood loss estimation is used. Table III illustrates the difference between the use of BL(1)

TABLE IV. *Comparison of indices suggested to affect blood loss between patients receiving different i.v. fluid regimens. Blood loss BL(4) was used. Statistical tests all revealed no significant differences (ns) determined by* $P > 0.05$. *The systolic arterial pressure from every 10th min through each TURP was used to calculate a patient mean value. The comparison of average arterial pressures was then performed on patient means*

	Ringer's acetate ($n = 28$)	Dextran 40 ($n = 10$)	Statistics
Resection time (min)			
Median	40	65	Mann–Whitney
Range	25–90	35–70	*U* test
Weight of resectate (g)			
Median	21.5	27	Mann–Whitney
Range	8.5–60	10–34	
Blood loss/resection time in (ml min^{-1})			
Median	7.6	7.2	Mann–Whitney
Range	2.7–23.9	3.0–31.1	
Blood loss/resectate weight (ml g^{-1})			
Median	19.1	26.0	Mann–Whitney
Range	0.9–85.1	6.8–46.3	
Cancerous histology (*n*)	1	1	None performed
Average systolic arterial pressure (mm Hg)			
Mean	126.3	116.5	Unpaired *t*-test
SD	21.0	18	

and BL(4). It is seen that negative balances become exaggerated while positive balances (= absorptions) become underestimated by the use of BL(1) instead of (the more correct) BL(4).

The difference in fluid balance between the use of BL(1) and BL(4) in table III was significant ($P < 0.001$) both for Ringer's acetate solution and dextran (paired *t* test). When considering subgroups, the mean difference in fluid balance for patients who absorbed and those who bled (groups a + b) was 142 ml when receiving Ringer's acetate solution, but only 30 ml for group (c) ($P < 0.001$). In patients receiving dextran, the corresponding values were 178 and 73 ml (no statistics performed).

However, there was no statistical difference in fluid balance between the use of BL(1) and BL(4) in table III when the former blood loss was corrected by appropriate haemodilution factors (0.82 for patients who absorbed and those who bled and 0.87 for other patients receiving Ringer's acetate; 0.83 for all patients receiving dextran).

Reviewing table I, it may be suggested that patients receiving dextran bled more than those with Ringer's acetate supplementation. However, Mann–Whitney's test did not demonstrate any statistical differences when BL(1)–(4) were compared in those receiving dextran or Ringer's acetate. The blood losses of patients receiving the two different fluids are compared with respect to resection time, weight of resectate, histology and average systolic arterial pressure in table IV. No difference was found in any of these factors.

DISCUSSION

Calculation of blood loss and irrigating fluid balance are suitable means for the routine monitoring of patients undergoing TURP. They inform the clinician about physiological events before symptoms occur, giving an opportunity to treat complications early. Estimations of irrigating fluid balance, in particular, may be affected by a number of factors that can give rise to incorrect values (Madsen, Kuni and Naber, 1973). These include inaccurate estimates of irrigating fluid volume caused by variations in the labelled contents and spillage. It is imperative that these variations are minimized and the balance calculated meticulously to give the relevant information about the absorption of irrigating fluid.

This study shows that the calculation of blood loss, and the volumetric irrigating fluid balance, can be affected by the use of a preoperative reference B-Hb since the amount of lost plasma is underestimated. Although it can be argued that a preoperative reference B-Hb does not misinform the clinician about the absolute loss of haemoglobin and plasma proteins, B-Hb determinations during the operation are needed to obtain a correct fluid balance, and probably serve as a better guide in estimations of the electrolyte loss associated with the absorption of irrigating fluid. While repeated B-Hb sampling is possible only for research purposes, the clinician can use a haemodilution factor to correct measurements of blood loss.

When extradural anaesthesia is given and fluid regimens similar to those reported in this paper are used, a haemodilution factor for correction of blood loss may be obtained from table II. If Ringer's acetate solution is given as i.v. fluid supplementation, the undetected plasma loss is dependent on intraoperative complications such as increased bleeding or the absorption of irrigating fluid, or both. When patients experience such complications, an appropriate haemodilution factor is 0.90 for the intraoperative period.

Dextran 40 is known to produce marked haemodilution (Hint, 1968). Although dextran and Ringer's acetate were given in different amounts in this study, patients in whom irrigating fluid was not absorbed or in whom bleeding was not increased had more pronounced haemodilution when receiving dextran than when receiving Ringer's acetate. Patients in whom there was excessive bleeding or fluid absorption had similar degrees of haemodilution regardless of the i.v. fluid used.

It should be noted that, on admission, blood was withdrawn with the patient in the sitting position while the blood samples during TURP were drawn with the patient supine. The blood volume is lower in the sitting than in the recumbent position because of the increase in hydrostatic pressure in the legs and subsequent diffusion of plasma to the interstitial tissue (Mountcastle, 1974). This diffusion is liable to give a greater B-Hb in the sitting position, which probably accounts for some, or most, of the difference between BL(1) and BL(2).

In assessing the similar blood loss in patients receiving Ringer's acetate and dextran, it is important to know whether these patient groups were comparable in factors known to affect blood loss. Several authors have noted a correlation between resection time and blood loss (Desmond and Gordon, 1969; Perkins and Miller, 1969, Levin, Nyrén and Pompeius, 1981) which was also

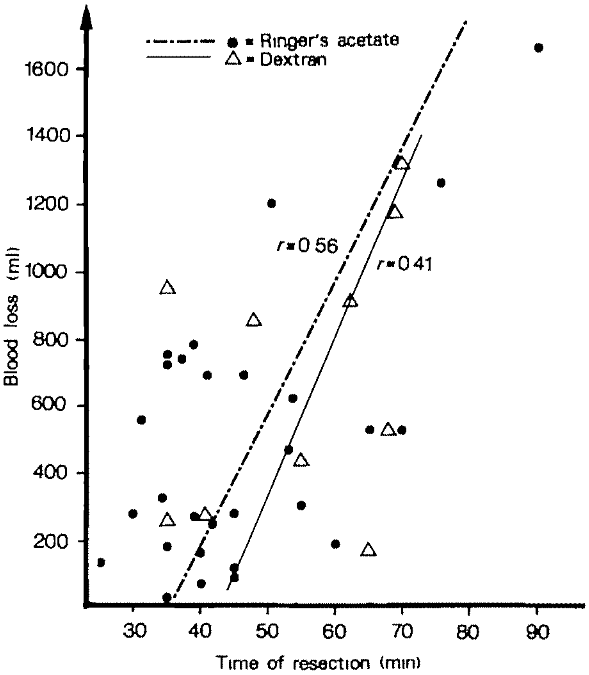

FIG. 1. The relation between resection time and blood loss BL(4). Correlation coefficients in simple regression analysis for Ringer's acetate and dextran are shown.

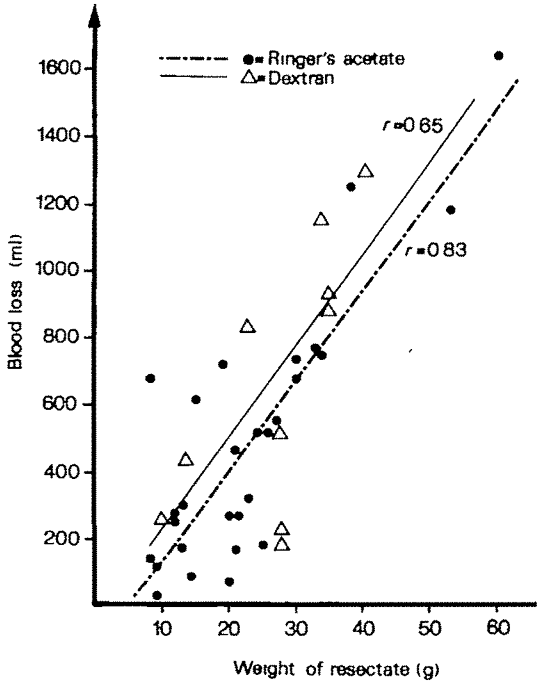

FIG. 2. The relation between weight of prostate resected and blood loss BL(4). Correlation coefficients in simple regression analysis for Ringer's acetate and dextran are shown.

found in this study (fig. 1). There appears to be a correlation between the weight of the resected prostatic tissue and blood loss (Cockett, Schultz and Franks, 1961; Perkins and Miller, 1969; Levin, Nyrén and Pompeius, 1981). A similar correlation was found in this study (fig. 2). Blood loss has been reported to be lower when the prostatic histology is malignant (Abrams et al., 1982), and suspected to correlate with the intraoperative arterial pressure (Madsen and Madsen, 1967). Although no difference could be found between patients receiving Ringer's acetate with respect to these variables (table IV), it should be remembered that the number of patients receiving dextran was small.

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EFFECTS OF UPPER OR LOWER ABDOMINAL SURGERY ON DIAPHRAGMATIC FUNCTION

B. DUREUIL, J. P. CANTINEAU AND J. M. DESMONTS

SUMMARY

Changes in abdominal (ΔAB) and rib cage (ΔRC) movements, and in vital capacity, were compared between 23 patients undergoing upper or lower abdominal surgery at 1, 3 and 7 days after surgery. Diaphragmatic index was obtained by measuring the relative abdominal motion ($\Delta AB/\Delta AB+\Delta RC$) using magnetometers. Electrical activity of abdominal muscles was assessed using needle electrodes after upper abdominal surgery in four additional patients. After upper abdominal surgery, the vital capacity and the diaphragmatic index were markedly reduced for 1 week. No abdominal muscle activity was observed at day 1. After lower abdominal surgery, the vital capacity returned to the normal range within 3 days of operation, without any diaphragmatic impairment. These findings substantiate the role of diaphragmatic dysfunction in postoperative reduction in vital capacity observed after upper abdominal surgery.

Patients undergoing upper abdominal surgery develop a restrictive pattern of pulmonary dysfunction (Craig, 1981). Vital capacity (VC) is reduced to approximately 40–50% of its preoperative value, and remains decreased for at least 1 week (Craig, 1981). This reduction in VC is associated with a marked decrease in functional residual capacity, arterial hypoxaemia and, frequently, lower lobe atelectasis. Although the mechanisms producing these effects are still under investigation, diaphragmatic dysfunction has been demonstrated after upper abdominal surgery (Ford et al., 1983; Simmoneau et al., 1983) and has been suspected to be the main determinant of these alterations in function. In contrast, much lesser changes in VC, and fewer pulmonary complications, are observed after lower abdominal surgery (Craig, 1981). It may, therefore, be interesting to compare the changes in diaphragmatic function and VC between patients undergoing upper or lower abdominal surgery.

PATIENTS AND METHODS

Twenty-seven patients undergoing abdominal surgery were selected; all were free from cardiorespiratory disease. Informed consent was obtained from each patient. In 23 patients, diaphragmatic function and VC were determined before, and after, the surgical procedure. This group was subdivided into two subgroups according to the site of surgery. Group 1 consisted of 17 patients undergoing upper abdominal surgery involving the biliary tract or the stomach through a midline incision. Group 2 consisted of six patients undergoing prostatectomy or hysterectomy through a midline suprapubic incision. In four additional patients undergoing upper abdominal surgery through a midline incision, the electrical activity of the abdominal muscles was measured after surgery. Characteristics of the patients are summarized in table I.

In 23 patients, VC was determined by spirometry, and the changes in the anterior–posterior dimensions of the ribcage (ΔRC) and abdomen (ΔAB) during quiet tidal breathing were measured with magnetometer coils, calibrated for linear distance (Mead et al., 1967) the day before surgery. The receiver coil for rib cage motion was placed anteriorly in the midline at the 4th or 5th intercostal space, the point of maximal observed motion. The receiver coil for abdominal motion was placed just above the umbilicus. Transmitter coils were placed at corresponding levels in the

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B. DUREUIL, M.D.; J. P. CANTINEAU, M.D.; J. M. DESMONTS, M.D.; Département d'Anesthésie-Réanimation, Hôpital Bichat, 46, rue Henri-Huchard, 75018 Paris, France. Accepted for Publication: February 16, 1987.

TABLE I. *Details of patients (mean values ± SEM). UAS = Upper abdominal surgery; LAS = lower abdominal surgery; BMI = body mass index (weight (kg) divided by the square of height (m)).* † *Values before operation*

	Age (yr)	BMI (kg m^{-2})	Duration of surgery (min)	Measured VC/ theoretical VC† (percent)	Diaphragmatic index†
Group 1 (UAS) ($n = 17$)	47±6	24.0±4.0	122±22	0.95±0.07	0.81±0.10
Group 2 (LAS) ($n = 6$)	46±6	26.9±3.5	120±42	0.92±0.09	0.83±0.11
Additional patients ($n = 4$)	46±8	25.6±3.0	130±28	–	–

midline of the back. For small anteroposterior changes in abdomen and ribcage, as observed during quiet tidal breathing, the magnetometer signals were linear. At least 10 quiet breaths were recorded at each assessment. Relative abdominal motion (the ratio ($\Delta AB/\Delta AB+\Delta RC$)) (Gilbert, Auchincloss and Peppi, 1981) was used as an index of the diaphragmatic contribution to the breathing process. A decrease in this index after surgery, from preoperative values, means that the contribution of the diaphragm to the breathing process is decreased (Gilbert, Auchincloss and Peppi, 1981). Measurements of VC and relative abdominal motion were carried out with the subjects in the supine position.

For the patients undergoing upper abdominal surgery, determinations of VC and of diaphragmatic index were repeated after surgery on days 1, 3 and 7. For the patients undergoing lower abdominal surgery, measurements were made on days 1 and 3. None of the patients had received opioids within the 6 h before measurements. In each group, data were compared using analysis of variance followed by paired comparison. The influence of the site of surgery was examined by an intergroup comparison using an analysis of variance in a factorial design. Values are given as mean ± SEM.

In the four additional patients, the electrical activity of the abdominal muscles was assessed 4 h and 24 h after the surgical procedure. All measurements were performed in the supine position. The subjects breathed through a mouthpiece attached to a pneumotachograph (Fleisch No. 3) connected to a pressure transducer (Validyne DP15) for measurements of flow and for the determination of inspiratory and expiratory time. Concentric unipolar needle electrodes were used to record the electrical activity (EMG) of the external oblique muscle. In two subjects, the EMG of the rectus abdominus was studied also. EMG signals were processed using an electromyograph preamplifier (DISA 15G01), filtered below 50 Hz and above 2000 Hz. After the first set of measurements, the positions of the needle electrodes were verified carefully to ensure a similar position for the set of measurements performed 24 h after surgery. None of these patients had received opioids within the 6 h before the second measurement.

RESULTS

There was no significant difference between the groups with respect to age, body mass index or duration of surgical procedure (table I). Values of VC (expressed as percent of predicted value) and diaphragmatic index were similar.

The changes in VC, induced by the surgical procedure, were expressed as a percent of control value and are shown in figure 1. After lower abdominal surgery, VC was reduced at day 1 and had returned to its preoperative value at day 3. After upper abdominal surgery, VC was markedly reduced from day 1 to day 7 and the decrease in VC was more marked after upper abdominal surgery than after lower abdominal surgery at day 1 and day 3. A typical tracing of changes in ΔAB and ΔRC before and after upper abdominal surgery, in one patient, is shown in figure 2. Variations in anteroposterior abdominal diameter for patients undergoing upper abdominal surgery were markedly reduced on days 1, 3 and 7, whereas no significant change in ΔRC was noted (table II). This marked decrease in ΔAB after upper abdominal surgery was accompanied by a significant decrease in diaphragmatic index on days 1, 3 and 7 (fig. 3). In contrast, after lower

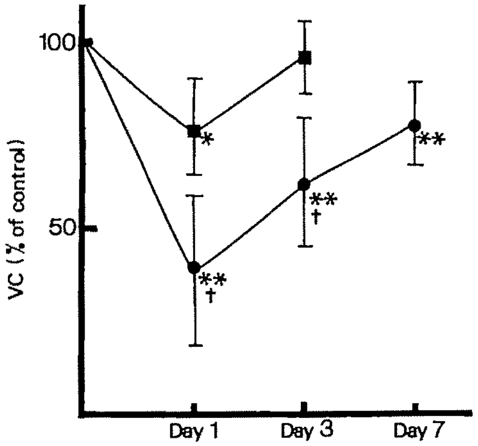

FIG. 1. Vital capacity (VC) (mean ± SEM) expressed as a percentage of preoperative value for the two groups. ■ = Lower abdominal surgery; ● = upper abdominal surgery. Significant difference from control: $^{*}P < 0.05$; $^{**}P < 0.01$. Significant difference between the two groups: $^{\dagger}P < 0.01$.

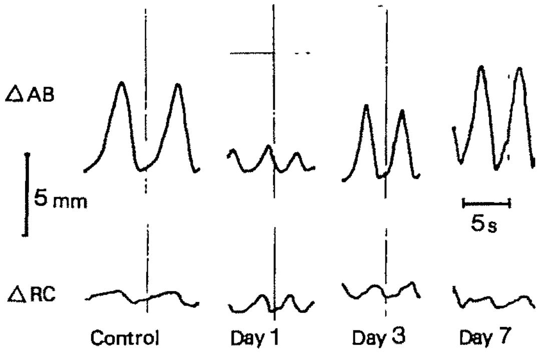

FIG. 2. Changes in pattern of breathing induced by upper abdominal surgery in one patient. Anteroposterior changes in abdominal diameter are markedly reduced at day 1 and day 3, with return to within control values by day 7.

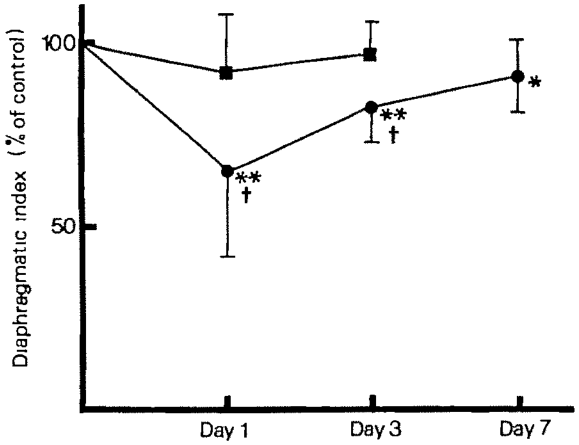

FIG. 3. Diaphragmatic index expressed as a percentage of the preoperative value for the two groups. ■ = Lower abdominal surgery; ● = upper abdominal surgery. Significant difference from control: $^{*}P < 0.05$; $^{**}P < 0.01$. Significant difference between the two groups: $^{\dagger}P < 0.01$. Bars indicate ± SEM.

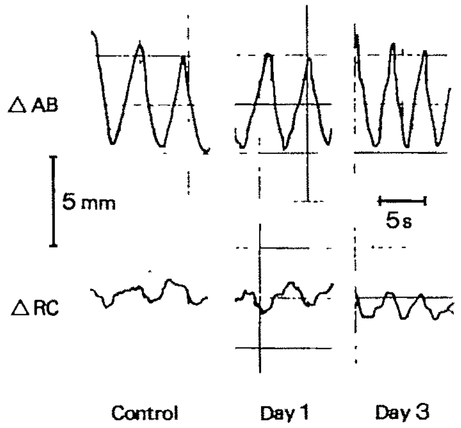

FIG. 4. Typical pattern of breathing in one patient before and after lower abdominal surgery.

abdominal surgery, abdominal and thoracic motions were unchanged, as shown for one patient in figure 4. No change in diaphragmatic index was observed for these patients (fig. 3). Consequently, the postoperative decrease in diaphragmatic index was significantly greater after upper than after lower abdominal surgery (fig. 3). Expiratory activity of the external oblique muscle was observed 4 h after the surgical procedure in two patients, and is illustrated by a typical tracing (fig. 5). In these patients, abdominal muscle activity was markedly reduced, to almost zero, 24 h after

TABLE II. *Mean values (±SEM) in anteroposterior changes of abdomen (ΔAB) and rib cage (ΔRC) in patients undergoing upper abdominal surgery. Significant difference from control*: $^{*}P < 0.05$; $^{**}P < 0.01$

	Control	Day 1	Day 3	Day 7
ΔAB (mm)	6.03±0.24	2.02±0.10**	2.46±10**	3.98±0.35*
ΔRC (mm)	1.41±0.09	1.23±0.04	1.170±0.04	1.29±0.05

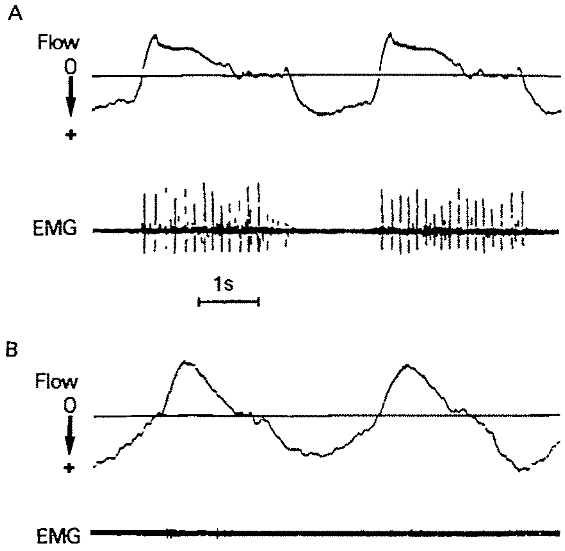

FIG. 5. Typical changes in air flow and in electrical activity (EMG) of external oblique muscle in one patient 4 h (A) and 24 h (B) after upper abdominal surgery.

the surgical procedure (fig. 5). In the remaining two subjects, there was no expiration activity in the external oblique, or the rectus abdominis, muscle 4 h and 24 h after surgery.

DISCUSSION

Our results confirm the occurrence of a marked decrease in VC and impairment of diaphragmatic function after upper abdominal surgery. In contrast, lesser changes in VC were observed after lower abdominal surgery, and diaphragmatic function remained within normal limits.

In this study, diaphragmatic function was assessed by using an index previously described by Gilbert, Auchincloss and Peppi (1981). However, additional factors, not related to an impairment of diaphragm function, might have affected this index also: active contraction of the abdominal muscles during expiration; changes in the mechanical properties of the abdominal compartment; mechanical interaction between rib cage and diaphragm.

In normal subjects, in the supine position, no activity of the abdominal muscles has been reported during quiet tidal breathing (Campbell, 1952). However, our present data demonstrate that expiratory abdominal muscle contraction may occur in man during the first few hours following upper abdominal surgery—as previously observed in dogs 1 h after cholecystectomy (Dureuil et al., 1985). At least two mechanisms may be involved in this early abdominal muscle activity. First, the residual effects of anaesthesia or the postoperative administration of opioids, or both, may play a role as Drummond, McCulloch and Brown (1984) have demonstrated that general anaesthesia increases abdominal muscle activity in man. Second, the effects of abdominal surgery on reflex pathways may also be involved. Indeed, stimulation of abdominal splanchnic afferents produces an increase in expiratory output (Albano and Garnier, 1983). Occurrence of strong abdominal activity during expiration followed by relaxation at the beginning of the next inspiration, would have changed relative abdominal motion via an increase in ΔAB even in the absence of changes in diaphragmatic function. This outward abdominal motion resulting from abdominal muscle relaxation would lead to an overestimate of the diaphragmatic contribution to the breathing process in the first few hours following surgery. However, no abdominal muscle activity could be detected during expiration 24 h after surgery using clinical (Simmoneau et al., 1983) or electromyographic assessment—as in the present study. These findings rule out a role of abdominal muscles in the genesis of the postoperative reduction in diaphragmatic index observed from day 1 to day 7.

Pneumoperitoneum, abdominal distension, or both, after operation may decrease abdominal compliance and so alter the mechanical properties of the abdominal compartment. These changes may reduce anteroposterior movement of the abdomen and thus affect the significance of the diaphragmatic index. However, no change in abdominal compliance was observed in dogs after cholecystectomy (Road et al., 1982). In addition, a decrease in abdominal wall compliance produces an increase in gastric pressure swings for the same diaphragmatic contraction. The fact that changes in gastric pressure, generated during inspiration, are reduced and even become negative after upper abdominal surgery (Ford et al., 1981; Simmoneau et al., 1983) suggests that marked diaphragmatic dysfunction is present, rather than an alteration in the mechanical properties of the abdominal compartment.

The last factor which could affect the use of the diaphragmatic index is the interaction between rib cage and diaphragm. Indeed, a decrease in this index could reflect increased ribcage activity as well as decreased diaphragmatic activity. However, in our study, the marked decrease in ΔAB, associated with little changes in ΔRC, suggests that strong diaphragmatic dysfunction had occurred after upper abdominal surgery, without any major change in intercostal activity. We can conclude that the diaphragmatic index used in the present study can be considered a reliable index of diaphragmatic function when assessed before and at least 24 h after abdominal surgery.

Two main mechanisms may be responsible for the alteration of diaphragmatic function following upper abdominal surgery (Ford et al., 1983): an alteration of the contractile properties of the diaphragm as a consequence of the surgical trauma and a reflex inhibition of phrenic nerve output via parietal or abdominal receptors. The first mechanism may be eliminated as no change in diaphragmatic contractility has been observed after upper abdominal surgery (Dureuil et al., 1986). Thus, a decrease in phrenic nerve output, secondary to surgery, may be considered as the main cause of the alteration in diaphragmatic function. Previous animal studies had shown that ventilatory muscle activity may be modified reflexly by stimulation of intra-abdominal sympathetic afferent nerves (Albano and Garnier, 1983) and that inhibition of phrenic nerve output occurred during mechanical stimulation of the gall bladder in dogs (Ford et al., 1983). However, the nature of the receptors—and of the afferent pathways involved—remains unknown in man. Since diaphragmatic function is unchanged after lower abdominal surgery, the role of parietal or peritoneal receptors should not be of major importance. Although a role for nocioceptors has been suggested, extradural analgesia with fentanyl failed to improve diaphragmatic function after upper abdominal surgery (Simmoneau et al., 1983). By contrast, thoracic extradural analgesia with bupivacaine produced a marked improvement in diaphragmatic function associated with an increase in VC (Mankikian et al., 1985). This effect, when local anaesthetic is used, could be related to the blockage of sympathetic abdominal receptors, stimulated previously during the surgical procedure and responsible for the phrenic nerve inhibition (Albano and Garnier, 1983).

The reduction in lung volume observed after upper abdominal surgery may be related to diaphragmatic dysfunction after surgery, as it has been reported in patients with bilateral diaphragmatic paralysis (Newsom-Davis, 1979). Since VC is a measurement obtained from a voluntary manoeuvre in which diaphragmatic muscle is the major contributor (Bates, Macklem and Christie, 1971), any alteration in diaphragmatic muscle function affects the outcome of this manoeuvre. After upper abdominal surgery, diaphragmatic strength is reduced during maximal inspiratory manoeuvres and this reduction may account for the postoperative decrease in VC (Simmoneau et al., 1983). Nevertheless, VC does not depend only on ventilatory muscle activity, but also on the mechanical properties of the lungs. The decreases in lung compliance observed after upper abdominal surgery may be implicated as a cause of the decreased postoperative VC. However, the decrease in pulmonary compliance is moderate, within 10–15% of the preoperative value (Okinaka, 1966). Therefore, this decrease in lung compliance which is observed for at least 1 week after surgery cannot be regarded as the major determinant of the 50% decrease in VC after operation.

Finally, a decrease in diaphragmatic motion results in a diminished ventilation and expansion of the lower parts of the lungs (Loh, Hughes and Newsom-Davis, 1979). This alteration might be involved in the occurrence of small airways closure and atelectasis of the lung bases following upper abdominal surgery. In contrast, diaphragmatic function is not altered after lower abdominal surgery and therefore the ventilation of the lung bases is probably unchanged. The lower incidence of pulmonary complications after lower than after upper abdominal surgery (Ali et al., 1974) could be related to the absence of diaphragmatic impairment after the former. Since the occurrence of pulmonary complications is related to the reduction in lung volumes (Ali et al., 1974), it would be interesting to assess whether the therapeutic improvement of postoperative diaphragmatic function may reduce their incidence after upper abdominal surgery.

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AN EVALUATION OF PRIMING WITH VECURONIUM†

M. SOSIS, A. STINER, G. E. LARIJANI AND A. T. MARR

Recently, a technique for facilitating rapid tracheal intubation — with the aid of non-depolarizing neuromuscular blocking drugs — has been described by Schwarz and colleagues (1985) using vecuronium. This method (priming) consists of the administration of a small dose of non-depolarizing blocker before induction, allowing sufficient time for the drug to reach the receptors and then the administration of a second larger dose after induction of anaesthesia to facilitate intubation. A suitable priming dose should allow the patient to maintain adequate ventilation and protect his airway. It should be well tolerated. In situations where suxamethonium is contraindicted (Gronert and They, 1975; Durant and Katz, 1982) this technique, if confirmed, would be a major advance.

This study was designed to compare the efficacy of priming with vecuronium against suxamethonium, and a single bolus dose of vecuronium.

SUMMARY

Priming with vecuronium was evaluated in three groups of patients. Group 1 ($n = 10$) received tubocurarine 0.05 mg kg^{-1}, group 2 ($n = 19$) received physiological saline and group 3 ($n = 21$) received vecuronium 0.012 mg kg^{-1}. After 4 min maximum inspiratory pressure was measured. Anaesthesia was induced with thiopentone 6–8 mg kg^{-1} and controlled ventilation with nitrous oxide and oxygen via a face mask instituted. The ulnar nerve was stimulated at the wrist. At 5 min group 1 patients received suxamethonium 1.5 mg kg^{-1}, group 2 received vecuronium 0.072 mg kg^{-1}, and group 3 received vecuronium 0.060 mg kg^{-1}. Intubation was accomplished at 6.5 min in all patients in group 1, 89% in group 2 and 90% in group 3. Patients in group 1 had no twitch response to stimulation at the time of intubation. Mean T4:T1 ratios at 6.5 min were 0.82 in group 2 and 0.61 in group 3 ($P < 0.05$). Intubating conditions were excellent in all group 1 patients, and in 53% and 67% of groups 2 and 3, respectively. Two patients in group 3 did not tolerate the priming dose and many had subjective complaints. Four group 3 patients could not sustain head lift and five showed decreased inspiratory pressure. Priming did not improve intubating conditions when compared with a single bolus technique and was not well tolerated.

PATIENTS AND METHODS

Fifty adult patients (ASA class I and II) free from neuromuscular diseases, and receiving no medication affecting sensitivity to neuromuscular blocking drugs took part in this investigation, which was approved by the Institutional Review Board. All patients gave informed written consent. Patients with anatomical conditions that would make tracheal intubation difficult were excluded.

In a randomized, double-blind manner the patients were assigned to one of the following treatments given in a standard volume: group 1 ($n = 10$) tubocurarine 0.05 mg kg^{-1}; group 2 ($n = 19$) physiological saline; group 3 ($n = 21$) vecuronium 0.012 mg kg^{-1}.

After 4 min each patient was asked to lift his head for 5 s and maximum inspiratory pressure was measured to assess whether the patient could

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MITCHEL SOSIS, M.D., PH.D.; ALAN STINER, M.D.; GHASSEM E. LARIJANI, PHARM.D.; ALEXANDER T. MARR, C.R.N.A.; Department of Anesthesiology, Jefferson Medical College, Philadelphia, Pennsylvania, U.S.A. Accepted for Publication: February 11, 1987.

Correspondence to M.S., Thomas Jefferson University Hospital, Department of Anesthesiology, 10th and Walnut Streets, 414 Main Building, Philadelphia, Pennsylvania 19107, U.S.A.

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TABLE I. *Scoring of intubating conditions*

Class	Definition
Excellent	Easy and no reaction
Good	Slight vocal cord movement, jaw incompletely relaxed
Fair	Vocal and movement present, moderate reaction
Impossible	Intubation impossible without additional time

TABLE II. *The effects of tubocurarine, vecuronium or saline on maximum inspiratory pressure and ability to perform 5-s head lift. Significant difference from vecuronium:* *$P < 0.05$

Compound	Dose (mg kg^{-1})	Maximum inspiratory pressure change ≥ 30 cm H$_2$O (%)	Successful 5-s head lift (%)
Tubocurarine	0.05	0*	100
Saline	—	0*	100
Vecuronium	0.012	24	81

adequately protect the airway (Brand et al., 1977). Thiopentone 6–8 mg kg^{-1} was administered 4.5 min after the first injection. The lungs were ventilated with nitrous oxide and oxygen via a face mask. At 5 min, group 1 patients received suxamethonium 1.5 mg kg^{-1}, group 2 received vecuronium 0.072 mg kg^{-1} and group 3 received vecuronium 0.060 mg kg^{-1}, again in a standard volume.

After the administration of the thiopentone, a DigiStim II nerve stimulator (Neuro Technology, Inc., Houston, Texas) was used for train-of-four stimulation of the ulnar nerve at the wrist using supramaximal impulses of 0.2 ms duration at 2 Hz through subcutaneous needles. The resulting thumb twitch was measured using a Grass FT03C force displacement transducer and recorded on paper with a Grass Polygraph. At 6.5 min tracheal intubation was attempted by an experienced anaesthetist. Conditions for intubation were graded on the scale listed in table I. The train-of-four ratio was noted at 6.5 min, as was the time of maximal neuromuscular blockade. The twitch tension was within the range of the transducer used under these circumstances (Freund and Merati, 1973).

Multivariate analysis of variance, followed by Duncan's multiple range test and Fischer's exact probability test were performed to detect any significant differences in dependent variables between the groups. The critical level of significance chosen was $P < 0.05$. All results are expressed as mean ± SD.

RESULTS

The results of the study are summarized in tables II and III. There were no significant differences between the groups in terms of age, weight or sex. All the patients in groups 1 and 2 could sustain a 5-s head lift before induction. In group 3, 19% could not sustain the head lift. This difference did not achieve significance.

Maximum inspiratory pressure decreased by 30 cm H$_2$O or more in 24% of patients in group 3. No patient in groups 1 and 2 showed a decrease in maximum inspiratory pressure.

Intubation was successful in all patients in group 1 at 6.5 min, in 89% of patients in group 2 and in 90% of the patients in group 3. Intubation conditions were "excellent" in all patients in group 1, and in 53% and 67% of those in groups 2 and 3, respectively. They were rated as "good" in 21% of those in group 2 and 24% in group 3. In 16% of the patients in group 2, intubating conditions were rated as "fair".

At 6.5 min the mean train-of-four ratios were 0.82 ± 0.14 in group 2 and 0.61 ± 0.28 in group 3. This difference was significant. Both T1 and T4 were zero in group 1. The time to maximal blockade was 7.8 ± 0.1 min in group 1, 11.2

TABLE III. *The effects of suxamethonium and vecuronium given either as a bolus or in divided doses 5 min apart on intubation, T4/T1 at attempted intubation and time to maximal blockade (mean ± SD). Significant difference from vecuronium 0.072 mg kg^{-1}:* *$P < 0.05$*; significant difference from both vecuronium groups:* $P < 0.05$

Compound	Dose (mg kg^{-1})	Successful intubation (%)	T4/T1	Maximal blockade (min)
Suxamethonium	1.5	100	—	7.8 ± 0.1
Vecuronium	0.072	89	0.82 ± 0.14	11.2 ± 1.5
Vecuronium	0.012 + 0.060	90	0.61 ± 0.28*	10.6 ± 1.5

±1.5 min in group 2 and 10.6±1.5 min in group 3.

Two patients in group 3 became agitated and complained of ventilatory distress soon after receiving their priming dose. Anaesthesia was induced immediately in one. Most patients in group 3 had severe ptosis shortly after the priming dose and many patients found the experience unpleasant and required considerable reassurance.

DISCUSSION

Vecuronium is a non-depolarizing neuromuscular blocking drug with a duration of action between those of suxamethonium and pancuronium (Miller et al., 1984) in standard doses. Attempts to use vecuronium in place of suxamethonium for tracheal intubation have shown that, even at a dose of 0.2 mg kg^{-1}, the time to reach 100% neuromuscular blockage is longer than with suxamethonium 1.5 mg kg^{-1} (Bencini and Newton, 1984).

Anaesthetists have long known that small doses of non-depolarizing blockers, as are used to prevent post-suxamethonium myalgia, are generally tolerated by awake patients, although occasional adverse reactions have been reported (Rogoff, Lippman and Walts, 1974; Engbaek and Viby-Mogensen, 1984).

Paton and Waud (1967) have shown that at least 70% of the receptors at the neuromuscular junction must be occupied before depression of the single twitch will occur, although tetanic fade will occur at lower levels of receptor occupancy. In an attempt to speed the onset of non-depolarizing drugs, priming has been advocated (Foldes, 1984; Doherty et al., 1985; Mehta et al., 1985; Schwartz et al., 1985).

In a pilot study, we attempted to determine the maximum priming dose that would be tolerated by awake, unpremedicated patients as determined by ability to sustain 5-s head lift. We found that 30% of patients receiving vecuronium 0.015 mg kg^{-1}, as suggested by Foldes (1984) and Schwarz and colleagues (1985), could not tolerate this dose. This is hardly surprising, since this is the ED_{50} of vecuronium (Fisher et al., 1982).

Brand and colleages (1977) have demonstrated the importance of head lift and inspiratory pressure in assessing recovery from neuromuscular blockade. Viby-Mogensen, Jorgensen and Ording (1979), Pavlin, Holle and Schoene (1982), and Lennmarken and Lofstrom (1984) have stressed the usefulness of head lift as a sign that the trachea can be extubated and the patient left with little supervision. The present study has shown that the incidence of inability to sustain 5-s head lift was reduced to 19% by decreasing the dose of vecuronium to 0.012 mg kg^{-1}. However, at this dose, 24% of our patients showed decreases of at least 30 cm H_2O in maximum inspiratory pressure.

Krieg and colleages (1980) showed that vecuronium 0.072 mg kg^{-1} produced intubating conditions rated as "good" in six of 12 patients and "excellent" in the remaining six at 2 min after injection. Consequently, at 90 s, vecuronium 0.072 mg kg^{-1} would yield sub-optimal intubating conditions. Therefore, any improvement conferred by priming on intubating conditions would be clearly seen.

Our results, using vecuronium 0.012 mg kg^{-1} given 5 min before 0.06 mg kg^{-1}, showed no improvement in intubating conditions, and a slightly lower train-of-four ratio when compared with a bolus of 0.072 mg kg^{-1}. We disagree with Schwarz and colleagues (1985) that the "divided dose method of administration compensates for the relatively slow onset of action of vecuronium (and)...provides excellent conditions for tracheal intubation just as rapidly as SCh" (suxamethonium).

We are surprised that the 10 premedicated awake patients studied by Schwarz and colleagues (1985) who received vecuronium 0.015 mg kg^{-1} "experienced no discomfort during the 3–4 minutes that elapsed until the administration of thiopental." They reported a train-of-four ratio of 0.77±0.03 (SEM) 5 min after a priming dose of vecuronium 0.015 mg kg^{-1}. They did not list the range of values found and we speculate that some of their patients would have had ratios considered too low for awake patients. Their group of 17 patients who received vecuronium 0.015 mg kg^{-1} showed twitch tensions averaging 84.7% of control, demonstrating that the "margin of safety" (Paton and Waud, 1967) had been exceeded.

Engbaek and colleagues (1985) noted train-of-four ratios of 0.57, 0.58, 0.59 and 0.82 and considerable subjective symptoms in four patients who received vecuronium 0.015 mg kg^{-1}. They concluded that doses larger than 0.010 mg kg^{-1}, the ED_{10} (Fisher et al., 1982), are not well tolerated by awake patients and they reported a patient in whom 0.005 mg kg^{-1} caused a dangerous degree of paralysis.

We agree with Schwarz and colleagues (1985) that all patients receiving a priming dose should be watched carefully and that anaesthesia should be induced rapidly if patient intolerance occurs. This is in marked contrast to the administration of a small dose of non-depolarizer before suxamethonium, since the 0.05-mg kg^{-1} dose administered to group 1 patients represents less than the ED_{10} of tubocurarine (Donlon et al., 1980). We cannot agree with Schwarz and colleagues (1985) that a marked reaction to a priming dose in an awake patient is a useful sign. Extreme sensitivity to neuromuscular blocking drugs can be determined with a twitch monitor after the patient is asleep and the airway secured.

Katz (1967) and Pelikan, Tether and Unna (1953) have noted great variability in the response to tubocurarine. If non-depolarizing drugs are given to awake patients, a suitably small dose must be chosen to avoid patient discomfort and, more importantly, the risk of aspiration (Musich and Walts, 1986). For vecuronium this dose should certainly be no greater than 0.010 mg kg^{-1}. However, even the small improvement in T4/T1 noted here is expected to be decreased if the priming dose is diminished.

In summary, this study has shown that priming with vecuronium produced no improvement in intubating conditions when compared with a single bolus technique. Priming is complicated, time consuming and, more significantly, may alarm the patients and conceivably put them at risk of aspiration.

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VECURONIUM OR SUXAMETHONIUM FOR RAPID SEQUENCE INTUBATION: WHICH IS BETTER?

C. MARTIN, J.-J. BONNERU, J.-P. BRUN, J. ALBANESE AND F. GOUIN

SUMMARY

The effects of suxamethonium, and of vecuronium given after three subparalysing (priming) doses, on the time of onset of neuromuscular blockade and on the resultant intubating conditions were compared. This study involved five groups of 10 patients (ASA class I or II) who were premedicated with flunitrazepam 0.015 mg kg^{-1} i.m. Anaesthesia was induced with thiopentone 6 mg kg^{-1} and fentanyl 0.003 mg kg^{-1}. In groups 2, 3 and 4 the patients were given a priming dose of vecuronium 0.01, 0.015 and 0.02 mg kg^{-1}, respectively. Three minutes later the intubating dose of vecuronium was given: 0.1 mg kg^{-1} (group 1), 0.09 mg kg^{-1} (group 2), 0.085 mg kg^{-1} (group 3), 0.08 mg kg^{-1} (group 4). When the electromyographic response was 95% of control, the trachea was intubated. In groups 2, 3 and 4, the onset time was significantly decreased compared with group 1. Increasing the priming dose from 0.01 mg kg^{-1} did not offer any advantage. The duration of blockade (time from the intubating dose to 15% recovery) was not significantly increased with any priming dose. In group 5, the trachea was intubated after suxamethonium 1.5 mg kg^{-1}. Mean onset time, which was significantly shorter than in the other groups, was half that of the groups that received a priming dose. Intubation conditions were better in group 5 than in the other groups ($P < 0.01$).

A rapid onset of action, allowing early tracheal intubation, is a desirable feature of a neuromuscular blocking drug, since it should decrease the risk of the aspiration of gastric content. Suxamethonium has this property, but has, unfortunately, a number of undesirable side effects (Walts, 1975). Vecuronium is a relatively short-acting non-depolarizing agent which has a relatively slow onset time (time from administration to 95 or 100% blockade) (Bencini and Newton, 1984). However, the onset time of vecuronium can be decreased by administration in divided doses (priming principle) (Clarke et al., 1985; Miller, 1985; Schwarz et al., 1985; Taboada, Rupp and Miller, 1986). In certain situations it is important that any reaction to the insertion of the tube is prevented so that there is no increase in intra-abdominal or intracranial pressure. This study was designed to compare the rates of onset of suxamethonium and vecuronium, the latter being given in divided doses. Special attention was paid to intubating conditions to determine which drug regimen was the better in this regard.

PATIENTS AND METHODS

After informed consent was obtained, 50 healthy patients (ASA class I or II) were included in the study. There were 27 men and 23 women (mean age ± SEM 48 ± 7 yr; range 23–72 yr); all were undergoing abdominal surgery.

Patients were premedicated with flunitrazepam 0.015 mg kg^{-1} i.m., approximately 45 min before the induction of anaesthesia with thiopentone 6 mg kg^{-1} and fentanyl 0.003 mg kg^{-1}. Increments of thiopentone (25 mg) were given if the eyelid reflex was not abolished. Anaesthesia was maintained with 70% nitrous oxide in oxygen. Neuromuscular function was monitored using electromyograms (Relaxograph monitor). The

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CLAUDE MARTIN, M.D.; JEAN-JACQUES BONNERU, M.D.; JEAN-PAUL BRUN, M.D.; JACQUES ALBANESE, M.D., FRANÇOIS GOUIN, M.D.; Département d'Anesthésie-Réanimation, Hôpital Sainte-Marguerite, 270, Boulevard de Sainte-Marguerite, 13277-Marseille Cedex 9, France. Accepted for Publication: February 13, 1987.

TABLE I. *Patient data. No significant differences were noted between the groups* ($P > 0.05$). *†Priming/intubating doses*

	Neuromuscular block at intubation (%)	No. of patients	Age (yr) (mean ± SEM)	Weight (kg) (mean ± SEM)
Group 1 Vecuronium 0/0.1 mg kg^{-1}†	95–100	10	53 ± 4	69 ± 2
Group 2 Vecuronium 0.01/0.09 mg kg^{-1}	95–100	10	53 ± 4	61 ± 3
Group 3 Vecuronium 0.15/0.85 mg kg^{-1}	95–100	10	55 ± 4	60 ± 3
Group 4 Vecuronium 0.20/0.80 mg kg^{-1}	95–100	10	60 ± 3	59 ± 3
Group 5 Suxamethonium 0/1.5 mg kg^{-1}	95–100	10	57 ± 3	66 ± 3

ulnar nerve was stimulated supramaximally at the elbow using two surface electrodes. Trains-of-four, with square pulses of 0.1 ms duration, at a frequency of 2 Hz, were repeated every 20 s. Electromyograms of the abductor digiti minimi were recorded from two surface electrodes. An indifferent electrode was interposed between the stimulating and the recording electrodes. In this study, the first evoked compound action potential was used and neuromuscular blockade was expressed as a percentage of baseline (preinjection) value (Lam and Cass, 1981). Integrated electromyography has been demonstrated to be convenient and reliable for monitoring non-depolarizing drugs during the onset and recovery phases, and for monitoring depolarizing drugs during onset (Weber and Muravchick, 1986).

Once a stable electromyographic response was obtained a priming dose of vecuronium was given after randomization (patient data are shown in table I): 0.0 mg kg^{-1} (group 1); 0.010 mg kg^{-1} (group 2); 0.015 mg kg^{-1} (group 3); 0.020 mg kg^{-1} (group 4). An additional group of 10 patients (group 5) received no priming dose. In this group intubation of the trachea was facilitated with suxamethonium 1.5 mg kg^{-1}. Three minutes after the priming dose the patients received the intubating dose of vecuronium: 0.1 mg kg^{-1} (group 1); 0.09 mg kg^{-1} (group 2); 0.085 mg kg^{-1} (group 3); 0.080 mg kg^{-1} (group 4). Vecuronium was made up to a volume of 10 ml and administered i.v. over 5 s via a fast flowing infusion. The anaesthetist undertaking the intubation of the trachea did not know which drug had been administered to the patient. Intubation was performed after 95% depression of the electromyographic response had occurred. No additional drugs were given before intubation. Onset times (times from the intubating dose to 95% depression) were measured. Intubating conditions were scored as follows: excellent (jaws relaxed, vocal cords apart and immobile, no diaphragmatic movement), good (same conditions except slight coughing), poor (cords moving, moderate coughing, bucking), not possible (cords closed). The clinical duration of blockade was measured also (time from the intubating dose to 15% recovery).

Two-way analysis of variance, Student, Newman–Keuls tests and Fisher's exact probability test were used to determine the significance of differences between groups. The null hypothesis was rejected at $P < 0.05$.

RESULTS

The time to intubation was significantly reduced ($P < 0.02$) by each priming dose of vecuronium (table II). Increasing the priming dose to more than 0.01 mg kg^{-1} had no influence on the onset time.

Intubation time was significantly shorter ($P < 0.01$) after suxamethonium (group 5) than in the other groups (table II). The size of the priming

TABLE II. *Intubation time (mean ± SEM) and clinical duration for groups of patients receiving different priming doses and intubating doses of vecuronium (groups 1–4) or suxamethonium (group 5)* (n = *10 in each group*). *$P < 0.02$ *compared with group 1*; **$P < 0.01$ *compared with other groups*

	Intubation time (s)	Clinical duration (s)
Group 1 Vecuronium 0/0.1 mg kg^{-1}	220 ± 20	1714 ± 163
Group 2 Vecuronium 0.01/0.09 mg kg^{-1}	165 ± 15*	2336 ± 210
Group 3 Vecuronium 0.015/0.085 mg kg^{-1}	158 ± 12*	2216 ± 326
Group 4 Vecuronium 0.02/0.08 mg kg^{-1}	141 ± 12*	2092 ± 190
Group 5 Suxamethonium 1.5 mg kg^{-1}	67 ± 8**	—

TABLE III. *Intubation conditions in the five groups.* *$P < 0.01$ *with groups 1, 2, 3, 4 and* $P < 0.05$ *with groups 2, 3, 4*

	Excellent	Good	Poor	Not possible
Group 1	3	5	2	0
Group 2	6	3	1	0
Group 3	7	3	0	0
Group 4	6	4	0	0
Group 5	9*	1	0	0

dose did not modify the clinical duration. Intubating conditions were excellent in three patients in group 1, in six or seven patients in groups 2, 3 and 4, and in nine patients in group 5. The best intubating conditions were observed in group 5 (table III).

DISCUSSION

Several regimens have been tested to obtain rapid tracheal intubation. Suxamethonium is currently the drug of choice and allows good intubating conditions in approximately 60–90 s when given at a dose of 1–1.5 mg kg^{-1} (Blitt et al., 1981; Bencini and Newton, 1984). However, its use is associated with certain undesirable effects such as malignant hyperthermia, increased intraocular pressure, hyperkalemia and postoperative muscle pain (Katz and Katz, 1975). Nevertheless, in most patients the drug is safe and its advantages (short onset of action, smooth intubating conditions) largely overcome its disadvantages (Lee, 1985).

In this study, the onset time of suxamethonium was 67 s and intubating conditions were excellent in nine out of 10 patients. These results were obtained with doses of 1.5 mg kg^{-1} and are similar to those reported by Bencini and Newton (1984). The use of smaller doses (0.6 mg kg^{-1}) results in a longer onset time (96 s) and if patients are intubated after 66 s, the neuromuscular response is 15–20% of control and intubating conditions are excellent in only two-thirds of the patients (Schwarz et al., 1985). Another point to consider is that, in this study, suxamethonium was given 3 min after the induction agents. Should it have been given immediately after the induction agents, the intubating conditions would certainly have been excellent in all of our patients because of the deeper anaesthesia.

Another way to achieve a short onset time is to use larger doses of non-depolarizing drugs. These doses are accompanied by serious side effects such as tachycardia with pancuronium (Miller et al., 1975) or hypotension with atracurium (Payne and Hughes, 1981). With the recommended dose of vecuronium (0.1 mg kg^{-1}) the time of onset of 95–100% blockade is 3 min (Bencini and Newton, 1984; Taboada, Rupp and Miller, 1986). As previously reported the onset of vecuronium is dose dependent and increased doses could result in a shorter onset time. "Large" intubating doses of vecuronium can be considered since this drug is almost entirely free from cardiovascular side effects (Barnes et al., 1982). Increasing the dose of vecuronium from 0.1 mg kg^{-1} to 0.15 mg kg^{-1} decreases intubation time by 1 min (Bencini and Newton, 1984). However, a further increase from 0.15 mg kg^{-1} to 0.2 mg kg^{-1} does not decrease the onset time (Agoston et al., 1980; Bencini and Newton, 1984). Intubating conditions are excellent, but the decrease in onset is offset by an increase in the duration of the action. In any case, the intubating time is never as short as after suxamethonium (Bencini and Newton, 1984). The use of a priming dose has been recommended to decrease the onset time of vecuronium (Clarke et al., 1985; Schwarz et al., 1985). In our patients the onset time was decreased significantly, from 3.5 to 2.5 min with any priming dose and this confirms the results of Taboada, Rupp and Miller (1986).

Increasing the priming dose from 0.01 mg kg^{-1} does not improve the onset time and it has been well documented that subjective side effects are increased, even in healthy individuals (Pelikan, Tether and Unna, 1953; Engbaeck et al., 1985; Taboada, Rupp and Miller, 1986). In all of our patients receiving vecuronium the onset times were longer than in the patients receiving suxamethonium. With the optimal priming dose (0.01 mg kg^{-1}) and a 3-min time interval, the onset time was twice that of the suxamethonium group. In the study of Schwarz and colleagues (1985) the use of divided doses of vecuronium produced the same onset time as suxamethonium. Possible reasons for this disparity were the use of large priming doses (0.015 and 0.020 mg kg^{-1}), a longer time interval (6 min) and smaller doses of suxamethonium (0.6 mg kg^{-1}). Intubating conditions were excellent in only six to seven of our patients when intubation was performed after vecuronium. Intubation scores were better in the suxamethonium group, the trachea being intubated under the same level of anaesthesia. Agoston and colleagues (1980) reported better intubating conditions with vecuronium. One explanation could be the wide variation in sensitivity of patients to these drugs (Katz and Katz, 1975). Another explanation is that our patients were intubated under light anaesthesia, since induction agents were given 3 min before the neuromuscular blocking drug. A final reason is that we used very stringent criteria for "excellent conditions": no response at all to the insertion of the tracheal tube.

In conclusion, when rapid sequence intubation is needed, suxamethonium 1.5 mg kg^{-1} produces a faster onset time and better intubating conditions than vecuronium used with any priming dose. In patients in danger of aspiration of gastric content, suxamethonium minimizes the period of vulnerability to aspiration. One disadvantage is that the increase in abdominal pressure could facilitate regurgitation. However, the priming principle is not innocuous in that regard and one case of pulmonary aspiration has been reported recently after the use of this technique (Musich and Walts, 1986).

It has also been demonstrated that the increase in gastric pressure produced by suxamethonium as a result of muscle fasciculation is accompanied by a correspondingly greater increase in lower oesophageal pressure, resulting in an increase in barrier pressure. There is thus no tendency to regurgitation in normal subjects (Smith, Dalling and Williams, 1978).

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INFLUENCE OF "PRIMING" ON THE POTENCY OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKING AGENTS

M. M. BRADY, R. K. MIRAKHUR AND F. M. GIBSON

SUMMARY

Dose–response curves have been constructed to determine the ED_{50} and ED_{95} (doses required to produce a 50% and a 95% block, respectively) following administration of a small "priming" dose of atracurium 50 µg kg^{-1}, vecuronium 10 µg kg^{-1} or pancuronium 10 µg kg^{-1}. The myoneural blockers were administered subsequently as a single bolus. The results were compared with previously published work on these drugs, in which no priming dose had been administered. The respective ED_{50} and ED_{95} values in the primed and control groups were 122 and 126 µg kg^{-1} and 208 and 226 µg kg^{-1}, respectively, for atracurium; 26 and 23 µg kg^{-1} and 42 and 39 µg kg^{-1}, respectively, for vecuronium; and 31 and 30 µg kg^{-1} and 56 and 60 µg kg^{-1}, respectively, for pancuronium. The values showed no significant differences between the respective primed and control groups. Contrary to previous suggestions, our results show no enhancement of blockade when these drugs were administered in divided doses.

It has been suggested that the onset of action of non-depolarizing neuromuscular blocking drugs can be accelerated by "priming"—the administration of the agent in divided doses (Foldes, 1984; Doherty et al. 1985; Mehta et al., 1985; Schwarz et al., 1985; Black et al., 1986). In addition, it has been argued that the block produced by the administration of these drugs in divided doses may be more intense than when the same total dose is given as a single bolus (Foldes, 1984; Doherty et al., 1985; Schwarz et al., 1985; Black et al., 1986). However, at present there is no evidence to support the possible potentiation of effect in association with priming. This point has been investigated, in the present study, by constructing dose–response curves for atracurium, vecuronium and pancuronium after priming, and then comparing the results with those obtained previously in control (non-primed) groups (Gibson et al., 1985a, b; Gibson and Mirakhur, 1987).

PATIENTS AND METHODS

Seventy-eight adult patients (ASA grades I and II) undergoing elective surgery requiring the use of neuromuscular blockade were included in the study. The informed consent of the patients and the approval of the regional ethics committee were obtained. Patients were premedicated with diazepam 10–15 mg by mouth and anaesthetized with thiopentone 5–6 mg kg^{-1}, nitrous oxide in oxygen and fentanyl 4–5 µg kg^{-1}. Further smaller increments of fentanyl were given, as required. Ventilation was adjusted to maintain the end-tidal carbon dioxide concentration between 4.5 and 5.0%.

The ulnar nerve was stimulated percutaneously at the wrist using a peripheral nerve stimulator (Myotest) delivering supramaximal square wave stimuli of 0.2 ms duration at a frequency of 0.1 Hz. The resultant force of contraction of adductor pollicis was measured and recorded using a force displacement transducer and a neuromuscular

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M. M. BRADY, M.B., F.F.A.R.C.S.; F. M. GIBSON, M.B., F.F.A.R.C.S.; Department of Anaesthetics, The Queen's University of Belfast, Belfast, N. Ireland. R. K. MIRAKHUR, M.D., PH.D., F.F.A.R.C.S., Department of Clinical Anaesthesia, Royal Victoria Hospital, Belfast, N. Ireland. Accepted for Publication: April 10, 1987.

Correspondence to R.K.M.

function analyser (Myograph 2000). A preload of 300 g was applied throughout the study.

Following stabilization of the control twitch height for about 10 min patients were randomly allocated to receive atracurium, vecuronium or pancuronium. A priming dose of atracurium 50 µg kg^{-1}, vecuronium 10 µg kg^{-1} or pancuronium 10 µg kg^{-1} was administered. Four minutes later patients were given a single dose of atracurium 50, 100, 150 or 200 µg kg^{-1}, vecuronium 10, 20, 30 or 40 µg kg^{-1}, or pancuronium 10, 20, 30, 40 or 50 µg kg^{-1} to obtain dose–response data using a single dose method as described previously (Gibson et al., 1985a, b; Gibson and Mirakhur, 1987). The size of the increments of neuromuscular blocker was the same as in our previous studies of dose–response relationships in the absence of the priming doses. There were six patients in each of the subgroups. The maximum degree of blockade attained and the time taken to achieve this were recorded in each patient. The same drug was administered to each patient both for priming and, subsequently, as the main dose. The data were subject to arc–sine transformation as described by Armitage (1971) for responses involving the extreme end-points (0 and 100%) on the dose–response curves. Dose–response curves were constructed following regression analysis. The data were compared (using a t test) with our previously published results on potency estimates for each of the three drugs (Gibson et al., 1985a, b; Gibson and Mirakhur, 1987). These earlier studies had been carried out using exactly the same methodology, with the exception of administration of the priming doses.

TABLE I. *Physical characteristics*

	n	Age (yr ± SEM)	Weight (kg ± SEM)
Atracurium			
Primed group	24	48 ± 6.44	71 ± 5.49
Control group (Gibson et al., 1985a)	28	40 ± 6.68	65 ± 4.74
Vecuronium			
Primed group	24	44 ± 5.98	72 ± 6.54
Control group (Gibson et al., 1985b)	30	38 ± 3.12	67 ± 3.84
Pancuronium			
Primed group	30	48 ± 5.95	74 ± 5.54
Control group (Gibson and Mirakhur, 1987)	36	44 ± 5.52	66 ± 4.34

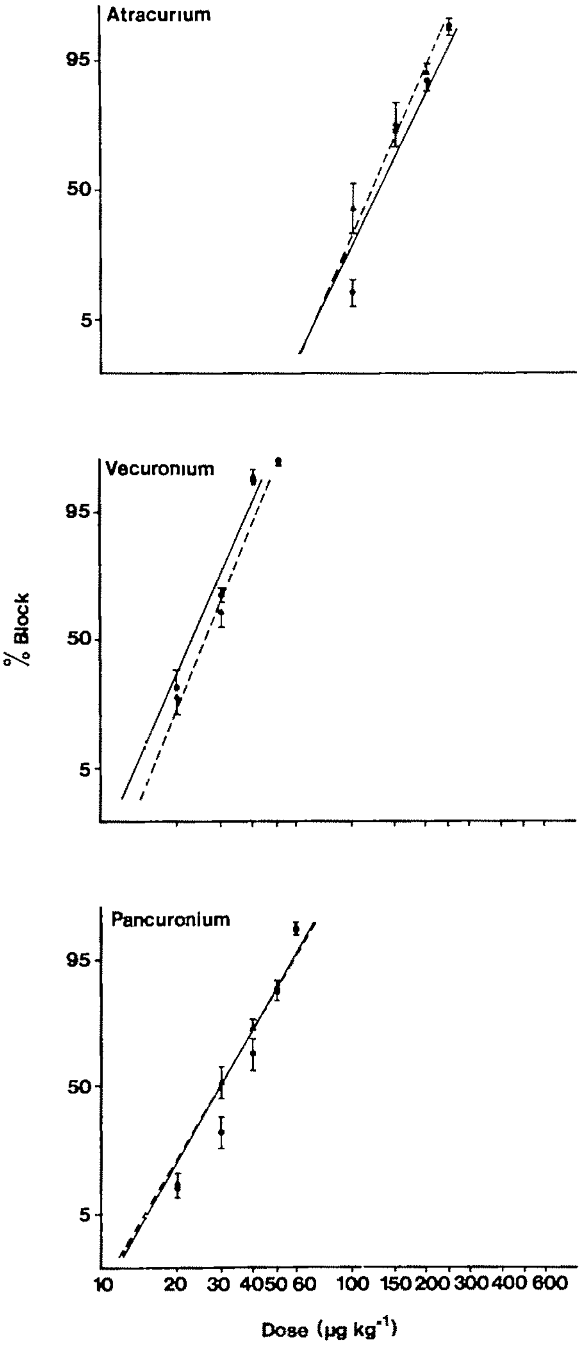

FIG. 1. Dose–response curves for atracurium, vecuronium and pancuronium in the primed (▲——▲) and control (non-primed, ●——●) groups. Data for control groups from Gibson and colleagues (1985a) for atracurium; Gibson and colleagues (1985b) for vecuronium; and Gibson and Mirakhur (1987) for pancuronium. Doses on the x-axis are on log-scale and responses following arc–sine transformation are on the y-axis.

TABLE II. *ED_{50} and ED_{95} values in the primed and control groups*

	ED_{50} (µg kg^{-1}) (95% confidence intervals)	ED_{95} (µg kg^{-1}) (95% confidence intervals)
Atracurium		
Primed group	122 (117–127)	208 (203–213)
Control group (Gibson et al., 1985a)	126 (115–137)	226 (207–246)
Vecuronium		
Primed group	26 (22–30)	42 (38–46)
Control group (Gibson et al., 1985b)	23 (20–26)	40 (36–43)
Pancuronium		
Primed group	31 (27–34)	56 (48–64)
Control group (Gibson and Mirakhur, 1987)	30 (24–36)	60 (48–72)

TABLE III. *Average maximum blockade following administration of various doses of the neuromuscular blockers in the primed and control groups. n = 6 for each subgroup except the vecuronium control group given 10 µg kg^{-1}, where n = 4). Data for control groups from: *Gibson et al. (1985a); †Gibson et al. (1985b); ‡Gibson and Mirakhur (1987). Ns = Not significant*

	Maximum block (% ± SEM)			Time taken to attain maximum block (min ± SEM)		
	Primed group	Control group	*P*	Primed group	Control group	*P*
Atracurium*						
50 µg kg^{-1}	—	—		—	—	
50 + 50 µg kg^{-1}	41 ± 10.11	16 ± 5.7	< 0.05	4.3 ± 1.37	6.6 ± 0.97	< 0.02
50 + 100 µg kg^{-1}	72 ± 13.08	70 ± 8.0	ns	6.3 ± 0.53	6.2 ± 0.69	ns
50 + 150 µg kg^{-1}	92 ± 2.29	88 ± 3.3	ns	5.5 ± 0.78	5.9 ± 0.43	ns
50 + 200 µg kg^{-1}	98 ± 1.36	98 ± 1.3	ns	4.8 ± 0.75	5.9 ± 0.86	ns
Vecuronium†						
10 µg kg^{-1}	—	—		—	—	
10 + 10 µg kg^{-1}	28 ± 10.28	31 ± 10.16	ns	2.9 ± 0.53	6.7 ± 0.48	< 0.001
10 + 20 µg kg^{-1}	62 ± 12.18	58 ± 8.0	ns	4.1 ± 0.47	6.1 ± 0.89	ns
10 + 30 µg kg^{-1}	96 ± 3.83	98 ± 1.02	ns	4.3 ± 0.64	4.9 ± 0.92	ns
10 + 40 µg kg^{-1}	98 ± 1.16	99 ± 0.49	ns	3.9 ± 0.55	4.5 ± 0.19	ns
Pancuronium‡						
10 µg kg^{-1}	—	2 ± 1.16	ns	—	7.9 ± 0.36	
10 + 10 µg kg^{-1}	13 ± 5.30	12 ± 5.96	ns	3.8 ± 0.31	7.8 ± 0.30	< 0.001
10 + 20 µg kg^{-1}	51 ± 9.99	32 ± 10.57	ns	4.9 ± 0.34	7.4 ± 0.81	< 0.02
10 + 30 µg kg^{-1}	76 ± 5.63	65 ± 11.59	ns	5.4 ± 0.28	8.5 ± 1.55	ns
10 + 40 µg kg^{-1}	89 ± 4.60	88 ± 6.08	ns	6.6 ± 0.74	8.4 ± 1.71	ns
10 + 50 µg kg^{-1}	99 ± 1.00	98 ± 1.67	ns	5.8 ± 1.49	6.1 ± 1.51	ns

RESULTS

The groups were comparable in their physical characteristics (table I), and these were similar to those of the patients in our previous studies in which the dose–responses were studied without priming.

The dose–response curves for atracurium, vecuronium and pancuronium are shown in figure 1. These did not differ significantly in their slopes, and the lines for primed and control groups were almost superimposed for each of the myoneural blockers. The actual calculated ED_{50} and ED_{95} values (doses producing 50% and 95% blockade, respectively) are given in table II, those for the control groups being from our previously published data. The calculated ED_{95} for the primed and the control groups were 208 and 226 µg kg^{-1}, respectively, for atracurium; 42 and 40 µg kg^{-1}, respectively, for vecuronium and 56 and 60 μg kg^{-1}, respectively, for pancuronium. These were not significantly different from each other, nor were the respective ED_{80} as given in table II.

The average maximum degree of blockade produced by each increment, and the times taken to achieve maximum blockade—whether given as a bolus or in divided doses—are shown in table III. It is clear that there were very few significant differences between the primed and the control groups in the degree of neuromuscular block produced, or the time to achieve blockade.

DISCUSSION

It has been suggested by Foldes (1984), Doherty and co-workers (1985) and Schwarz and colleagues (1985) that the degree of blockade produced by the administration of a given dose of vecuronium or pancuronium in divided doses produced a more intense degree of block than when the same dose was given as a single bolus. More recently, the same has been suggested by Black and colleagues (1986) in relation to alcuronium. However, the results from the present study demonstrate that the administration of any particular dose of atracurium, vecuronium or pancuronium produced the same degree of blockade whether given as a single bolus or in divided doses. It is difficult to find an explanation for potentiation with the use of myoneural blocking drugs in divided doses, on the basis of recently published work which compares the cumulative and single dose techniques. All show a significantly greater degree of blockade when atracurium or vecuronium were administered as a single bolus (Fisher et al., 1982; Katz et al., 1982; Gibson et al., 1985a, b) or, in the case of pancuronium, no difference (Gibson and Mirakhur, 1987). Obviously, the technique of priming is somewhat akin to a cumulative technique. A possible reason for the claims made by other workers for more intense blockade could be the use of relatively larger doses of neuromuscular blocking agents which produce close to complete blockade, under which circumstances it would be difficult to detect any differences in the degree of block produced. In addition, others have used different doses in primed and in control subjects (Taboada, Rupp and Miller, 1986). Although some of the previously published studies had shown some advantage of priming in terms of an acceleration in the onset of blockade, more recent studies, in which the same neuromuscular blocker has been administered for priming and for subsequent use, have failed to confirm these results (Ramsey et al., 1985; Weinberg, Stirt and Longnecker, 1985; Donati et al., 1986; Ramsey, Morell and Gerr, 1986; Brady et al., 1987). However, accelerated onset or potentiation of blockade may be expected, and has been observed, when different drugs are used for priming and subsequent administration; for example, tubocurarine or metocurine for priming and pancuronium or vecuronium for subsequent administration (Donati et al., 1986; Ramsey, Morell and Gerr, 1986). This is the result perhaps of the use of potentiating combinations of drugs based on their relatively different pre- and postjunctional effects.

It is not within the remit of this study to comment on the usefulness of priming technique, but it is likely that the only benefit is some improvement in the intubating conditions with the use of atracurium and vecuronium—as has been reported previously (Schwarz et al., 1985; Mirakhur et al., 1986). However, with doses of atracurium and vecuronium in the order of 0.5 and 0.1 mg kg^{-1}, respectively, one can intubate the trachea in the absence of a complete block (Mirakhur et al., 1983, 1985); thus this would not be a very discriminating technique with which to show the differences resulting from priming.

In conclusion, the results from the present study show that the administration of the same neuromuscular blocking drug in divided doses (the "priming" technique) is not associated with an increase in potency.

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CONTINUOUS I.V. INFUSION OF LABETALOL FOR POSTOPERATIVE HYPERTENSION

Haemodynamic Effects and Plasma Kinetics

M. CHAUVIN, H. DERIAZ AND P. VIARS

SUMMARY

Labetalol is a combined α- and β-adrenoreceptor blocking agent. A loading dose may be used to antagonize sympathetic overactivity rapidly after surgery and be followed by a continuous infusion to achieve a stable effect. The haemodynamic effects and pharmacokinetics of this method of labetalol administration were studied in six rewarmed, extubated and sedated patients 15±2 h after aortobifemoral bypass surgery. Patients were monitored with radial and thermistor-tipped pulmonary artery catheters. Labetalol 1.5 mg kg^{-1} was injected i.v. over 5 min and a maintenance infusion of 0.2 mg kg^{-1} h^{-1} was started 30 min later and continued for 5.5 h. Within 5 min of the loading dose, i.v. labetalol induced significant ($P < 0.05$) decreases in mean arterial pressure (−32±11%), in heart rate (−20±11%) and in cardiac index (−26±15%) that lasted throughout the infusion. Changes in systemic vascular resistance were not uniform, but an increase was not observed in any patient. Mean stroke volume index and ventricular filling pressures were not significantly affected by labetalol administration. The mean measured steady state plasma concentration (C^{ss}) (264±46 ng ml^{-1}) was higher than predicted (170 ng ml^{-1}) because the clearance (13.1±2.4 ml kg^{-1} min^{-1}) was lower than that used to calculate the infusion rate. We conclude that labetalol is an effective antihypertensive agent in the postoperative period. A C^{ss} can be achieved rapidly by such i.v. administration and this offers the advantage of inducing rapid and stable haemodynamic effects. However, calculation of the infusion rate must be based on a clearance of 13 ml kg^{-1}min^{-1}.

The maintenance of β-adrenoreceptor blockade is appropriate after surgery (Villers et al., 1984) when sympathetic overactivity occurs in patients with hypertension, coronary artery disease, or both. β-Adrenoreceptor blocking agents reduce the oxygen demand of the heart by decreasing the rate–pressure product and by depressing contractility. However, pure β-adrenoreceptor blocking agents increase systemic vascular resistance (SVR) because of a decrease in cardiac output (CO) and unopposed α-adrenoreceptor stimulation (Ulrych et al., 1968). Labetalol is a combined α- and β-adrenoreceptor blocking agent (Brogden et al., 1978) which may be of more value than propranolol in the acute treatment of hypertension. It has already been used at induction of (Fischler et al., 1985), during and after anaesthesia (Meretoja et al., 1980; Morel, Forster and Suter, 1982; Dagnino and Prys-Roberts, 1985). Pharmacodynamic and pharmacokinetic data on the i.v. infusion of labetalol during the postoperative period have been published (Dagnino and Prys-Roberts, 1985), but no study has been performed in which such data have been collected after a loading dose and maintenance infusion rate of labetalol.

PATIENTS AND METHODS

Six patients (mean age 57 yr, range 30–73, mean weight 64 kg, SD 9) underwent aortobifemoral bypass surgery. Informed consent was obtained from each patient. All patients were given diazepam 10 mg by mouth 2 h before induction of

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M. CHAUVIN, M.D., Département d'Anesthésie-Réanimation, Hôpital Ambroise Paré, 92100 Boulogne, France. H. DERIAZ, M.D.; P. VIARS, M.D.; Département d'Anesthésie-Réanimation, Hôpital de la Pitié-Salpétrière, 75013 Paris, France. Accepted for Publication June 26, 1986.

Correspondence to MC.

anaesthesia with fentanyl 50 ± 10 μg kg^{-1}, thiopentone 5 mg ± 1 mg kg^{-1}, flunitrazepam 15 ± 4 μg kg^{-1} and 60% nitrous oxide in oxygen. Pancuronium 0.15 ± 0.03 mg kg^{-1} was administered. Ventilation was controlled throughout anaesthesia and in the early postoperative period. Pulmonary artery and radial artery catheters were inserted before surgery for the continuous monitoring of haemodynamic variables. Four patients had preexisting arterial hypertension and two were being treated with a β-adrenoreceptor blocking agent (acebutolol 600 mg day^{-1} in one and propranolol 120 mg day^{-1} in the other). Of the other two hypertensive patients, one was receiving alpha-methyldopa 500 mg day^{-1} and frusemide 40 mg day^{-1} and the other, clonidine 450 μg day^{-1} and althiazide 15 mg day^{-1}. The last oral dose of their usual antihypertensive drug was administered to each patient within 2 h of anaesthesia. No patient presented clinical, radiological or ECG evidence of congestive heart failure or atrio–ventricular block. Blood urea and serum creatinine concentrations and liver function tests were all within their normal ranges.

The study was conducted 15 ± 2 h after the end of surgery when the patients were normothermic and once the trachea had been extubated. At the time of the study the patients had normal blood-gas tensions and adequate analgesia, which was produced by extradural morphine 0.05 mg kg^{-1} administered when pain appeared at least 4 h after the last systemic injection of narcotic. The persistence of a mean arterial pressure (MAP) greater than 120 mm Hg, associated with cardiac index (CI) greater than 2 litre min^{-1} m^{-2}, led to the decision to administer labetalol. A loading dose of labetalol 1.5 mg kg^{-1} i.v. was injected to a peripheral vein over 5 min. The procedure allowed for the loading dose to be stopped at 2 min if MAP decreased to less than 80 mm Hg. A maintenance infusion rate of 0.2 mg kg^{-1} h^{-1} was started 30 min later and maintained for 5.5 h. This infusion rate was calculated on the basis of a total body clearance (*Cl*) of 20 ml kg^{-1} min^{-1} (McNeil and Louis, 1984), in order to produce a C^{ss} of 170 ng ml^{-1} as follows (Mitenko and Ogilvie, 1972; Wagner, 1974): maintenance infusion rate = $C^{ss} \times Cl$.

The following haemodynamic variables were measured: MAP, heart rate (HR), right atrial pressure (RAP), pulmonary arterial pressure (PAP) and pulmonary artery wedge pressure (PWP). CO was determined by the thermodilution method. Cardiac index (CI), stroke volume index (SI), systemic vascular resistance (SVR), pulmonary vascular resistance (PVR) and left ventricular stroke work index (LVSWI) were calculated. Measurements were repeated before and 5, 15, 30, 60, 120, 180, 240, 300 and 360 min after the labetalol loading dose. Blood samples for plasma labetalol measurement were collected from the radial artery before the administration of labetalol, at the end of the injection of the loading dose and from then on, simultaneously with haemodynamic measurements. Blood samples were centrifuged immediately and the plasma and red cells separated. Plasma was stored at −25 °C. Plasma drug concentrations were measured by a fluorimetric method (Martin, Hopkins and Bland, 1976). Labetalol clearance was calculated by dividing the infusion rate by the measured C^{ss} for each patient.

Data were expressed as mean values ± SD. For statistical analysis, an analysis of variance and the Student's paired *t* test were used.

RESULTS

All patients received the full loading dose of labetalol. The haemodynamic data are summarized in figure 1 and table I and the individual results concerning CI and SI in table II and SVR in table III. At the time of the control measurements, CI was increased, but calculated SVR and right and left ventricular filling pressures were within their normal ranges. Labetalol i.v. induced a significant ($P < 0.05$) mean decrease in MAP (−32 ± 11%), in HR (−20 ± 11%) (fig. 1) and in CI (−26 ± 15%) (table II) within 5 min of the

TABLE I. *Effect of labetalol on mean values (±SD) of right atrial pressure (RAP), pulmonary arterial pressure (PAP) and pulmonary vascular resistance (PVR). C = before labetalol administration*

	C	5 min	15 min	30 min	1 h	2 h	3 h	4 h	5 h	6 h
RAP (mm Hg)	5±3	7±2	7±3	6±4	8±5	6±5	6±6	6±4	5±6	7±6
PAP (mm Hg)	21±5	19±6	18±5	18±5	18±4	20±6	19±4	20±5	21±7	22±6
PVR (mm Hg litre^{-1} min m^{-2})	2.4±0.6	2.2±0.4	2.2±0.6	2.5±0.3	2.6±0.8	3.0±1.1	2.7±0.8	3.2±0.6	3.3±0.9	2.8±0.4

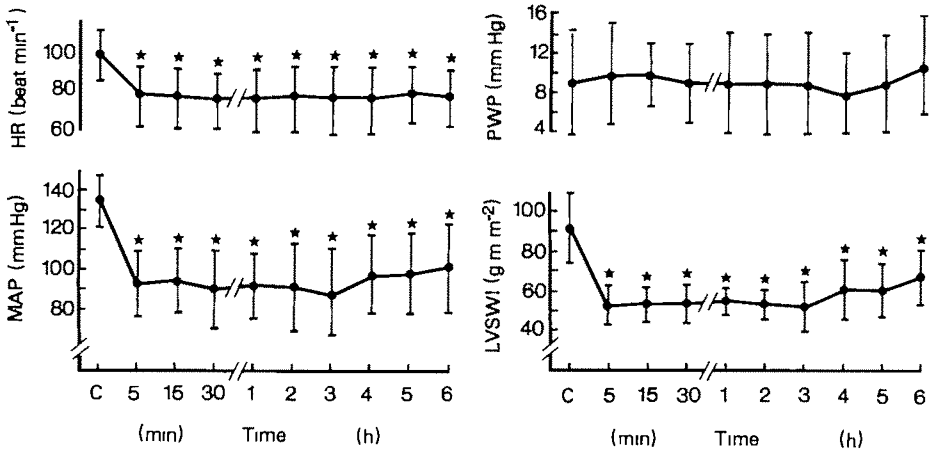

FIG. 1. Mean values (±SD) of heart rate (HR), mean arterial pressure (MAP), pulmonary artery wedge pressure (PWP), left ventricular stroke work index (LVSWI) before (C) and after the i.v. loading of labetalol 1.5 mg kg^{-1}. A maintenance infusion rate of 0.2 mg kg^{-1} h^{-1} was begun at time 30 min for 5.5 h. *Significantly different from C ($P < 0.05$).

loading dose and these changes persisted throughout the continuous infusion. A decrease in CI in all six patients was accompanied by a decrease in SI in patients 1, 5 and 6, but no change in the other three (table II). Within 5 min, the changes in SVR induced by labetalol were no longer uniform (table III), but at 3 h, SVR had decreased in all patients. The mean decrease in SVR (−22±16%) was significant ($P < 0.05$) (table III). Neither ventricular filling pressures

TABLE II. *Effect of labetalol on individual values of cardiac index (CI) (litre min^{-1} m^{-2}) and stroke volume index (SI) (ml beat^{-1} m^{-2}). C = before labetalol administration. Values of* P *are comparisons with C*

	C		5 min		15 min		30 min		1 h	
Patients	CI	SI	CI	SI	CI	SI	CI	SI	CI	SI
1	7.18	73.3	4.66	59.0	4.20	55.3	4.72	64.7	5.08	66.0
2	4.28	57.1	3.91	58.4	4.25	61.6	4.09	62.0	3.89	60.8
3	4.95	43.4	3.99	42.0	4.07	45.2	4.00	44.0	3.87	43.5
4	4.29	42.9	3.22	41.3	3.12	39.0	3.16	40.5	2.94	38.2
5	3.92	36.3	3.12	31.8	2.97	31.3	2.78	28.7	3.10	32.6
6	4.44	46.7	2.19	38.4	2.38	41.8	2.54	45.4	2.63	47.0
Mean	4.84	50.0	3.52	45.2	3.50	45.7	3.38	47.6	3.59	48.0
±SD	1.19	13.3	0.86	11.1	0.78	11.1	1.10	13.6	0.89	13.0
P			< 0.05		< 0.05		< 0.05		< 0.05	

	2 h		3 h		4 h		5 h		6 h	
Patients	CI	SI	CI	SI	CI	SI	CI	SI	CI	SI
1	4.85	59.1	5.51	70.6	5.24	68.9	4.89	61.1	4.81	66.8
2	3.81	59.5	4.35	69.0	3.73	59.2	3.94	61.6	3.91	57.5
3	4.08	43.4	4.59	46.8	4.81	50.6	4.80	50.0	4.89	49.9
4	3.34	41.8	3.30	41.3	2.90	37.2	3.15	41.4	3.52	46.3
5	2.89	29.2	3.13	32.6	3.24	32.4	3.26	33.3	3.41	36.3
6	2.88	50.5	2.57	42.8	2.82	46.2	2.72	40.6	2.94	44.5
Mean	3.64	47.3	3.91	50.5	3.79	49.1	3.79	48.0	3.91	50.2
±SD	0.76	11.6	1.09	14.3	1.02	13.6	0.90	11.6	0.79	10.7
P	< 0.05		< 0.05		< 0.05		< 0.05		< 0.05	

TABLE III. *Effect of labetalol on individual values of calculated systemic vascular resistance (SVR). C = before labetalol administration.* P *value is comparison with C*

	SVR (mm Hg litre^{-1} min m^{-2})									
Patients	C	5 min	15 min	30 min	1 h	2 h	3 h	4 h	5 h	6 h
1	17.1	18.5	18.9	15.0	14.2	15.2	10.9	15.0	18.2	16.8
2	28.0	15.0	16.7	16.3	17.0	17.7	15.4	17.7	17.8	17.1
3	25.8	24.3	24.8	26.3	25.1	25.5	22.0	23.1	22.9	24.3
4	35.0	32.0	33.0	31.0	34.0	32.0	30.0	30.0	33.0	31.0
5	32.6	30.8	31.6	32.7	28.7	34.6	30.7	30.5	31.0	32.0
6	29.0	31.8	31.2	29.3	30.4	23.5	25.1	30.9	31.1	31.8
Mean	27.9	25.4	26.0	25.1	24.9	24.8	22.4	24.5	25.7	25.2
±SD	6.2	7.4	7.0	7.6	7.8	7.7	7.9	7.0	6.9	7.2
P							< 0.05			

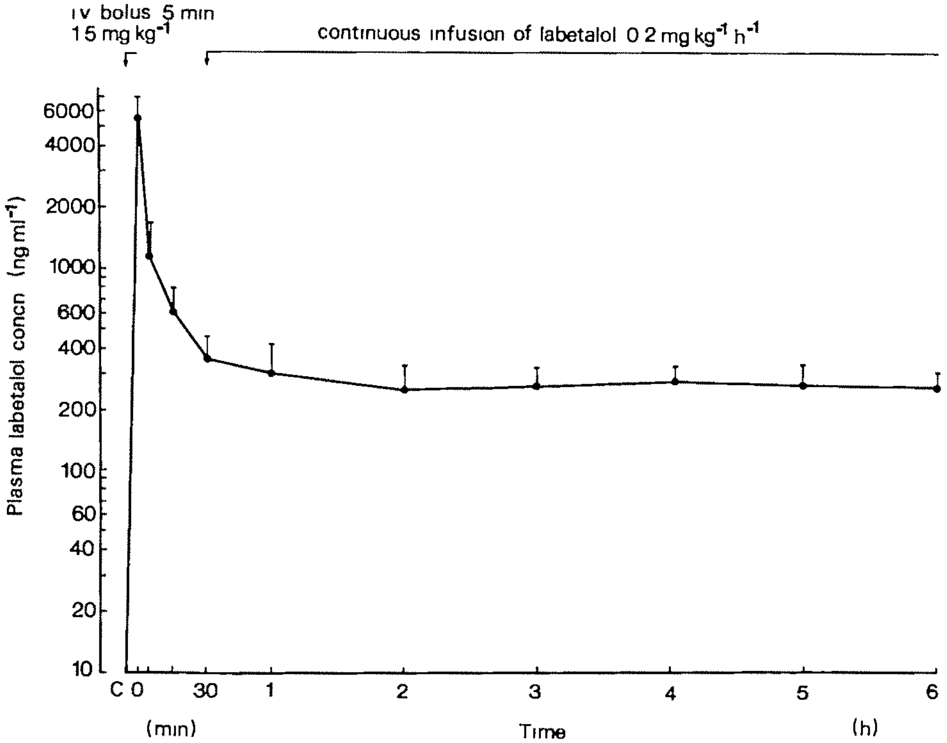

FIG. 2. Mean plasma labetalol concentration (±SD) collected during the study. C = before the i.v. loading dose of labetalol.

nor PVR were greatly affected by labetalol administration (fig. 1, table I). Labetalol reduced LVSWI by 40 % (fig. 1).

Plasma labetalol concentrations (fig. 2) decreased rapidly after the loading dose, but a stable mean concentration of 264±46 ng ml^{-1} was recorded within 2 h. There were no significant variations in plasma labetalol concentration between 2 and 6 h. The individual coefficients of variation of plasma concentrations measured between 2 and 6 h did not exceed 15 %. The labetalol clearance calculated under stable infusion conditions ranged between 10.9 and 15.9 ml kg^{-1} min^{-1} (mean 13.1±2.4). There was no correlation between the haemodynamic effects of labetalol and plasma concentrations.

DISCUSSION

Labetalol has been used previously in the treatment of postoperative hypertension (Meretoja et al., 1980; Morel, Forster and Suter, 1982; Dagnino and Prys-Roberts, 1985). However, the only study (Meretoja et al., 1980) which investigated the haemodynamic effects of labetalol in postoperative hypertension showed differences compared with reports of its use in essential hypertension (Koch, 1977; Dunn et al., 1983). The cardiac effects of labetalol in the present series are similar to those recorded in the previous study (Meretoja et al., 1980) after coronary artery surgery. It appeared to have the same features as other β-adrenergic blocking agents (Ulrych et al., 1968; Burt and Foëx, 1979). It reduced CI in direct proportion to the decrease in HR. Although mean SI was not significantly affected, it decreased in three patients and the decrease in LVSWI observed without a simultaneous reduction in PCWP in all the patients confirmed that labetalol decreased contractility (Meretoja et al., 1980). No increase in SVR was induced by labetalol. In contrast, when pure β-adrenergic blocking agents were injected i.v. the decrease in CO was associated with increased SVR (Ulrych et al., 1968; Burt and Foëx, 1979; Taylor, Silke and Lee, 1982). Contrary to what was seen by Meretoja and colleagues (1980) during the postoperative period, we noted systemic arteriolar dilatation in one of the six patients. This decrease in SVR agrees with the findings obtained after the acute administration of labetalol in hypertensive patients (Koch, 1977; Dunn et al., 1983). This is attributable to the additional property of labetalol (Brogden et al., 1978) which blocks the α-receptor increase induced by the β_2-blockade. This action of labetalol increases the antihypertensive effect produced by a decrease in CO. However, this α-blocking effect is weaker than the β-blockade and is consistent with animal studies which noted that labetalol is an α-adrenoreceptor antagonist two to seven times less potent than phentolamine (Farmer et al., 1972; Brittain and Levy, 1976) and with the reports in man where it was found that the β-adrenoreceptor blocking effect of the drug is greater than that of the α-adrenoreceptor action, in the ratio of approximately 3:1 (Richards, Tuckman and Prichard, 1976).

In the present study we started the labetalol administration after complete rewarming and we excluded patients with left ventricular dysfunction and hypovolaemia in order to avoid the deleterious haemodynamic effects of β-receptor blockade. All patients responded to the loading dose of labetalol and its efficacy may be explained in terms of their increased CI before treatment. This is consistent with the results of Morel, Forster and Suter (1982) who noted a more marked decrease in arterial pressure with labetalol in patients with increased sympathetic drive.

Despite its large volume of distribution (11 litre kg^{-1}) (McNeil and Louis, 1984), its high hepatic and total body clearance (McNeil and Louis, 1984) make labetalol a most suitable drug for continuous infusion (Dagnino and Prys-Roberts, 1985). However, a delay always exists between starting an infusion and the establishment of steady state conditions. This can be considered to occur in 3.3 half-lives (Rowland and Tozer, 1980) and would take approximately 13 h of constant infusion of labetalol to achieve. The bolus dose given before the start of the infusion enabled this to be attained more rapidly. Such a method has already been described for propranolol (Villers et al., 1984; McAllister, 1976), but never for labetalol. The loading dose was not selected on known pharmacokinetic values, it was an empirical dose used generally in clinical practice (McNeil and Louis, 1984); we obtained the peak effect within 5 min. Thirty minutes after this initial infusion, the slower infusion maintained a stable plasma concentration of the drug up to 6 h. The maintenance infusion rate was not started immediately after the loading dose in order to be sure that the maximal effect of the initial injection had been seen. It has been reported that a plasma concentration of 150–220 ng ml^{-1} is necessary to provide adequate beta-adrenoreceptor blockade (Prys-Roberts, 1984). On the basis of the pharmacokinetic results of previous studies, the correct infusion rate to maintain a C^{ss} of 170 ng ml^{-1} has been determined as 0.20 mg $\mathrm{kg}^{-1}\,\mathrm{h}^{-1}$ using the method described by Mitenko and Ogilvie (1972) and Wagner (1974). The calculated infused dose used in the present study maintained plasma labetalol concentration above the predicted value which indicates that the clearance value used to determine the maintenance infusion rate was not quite correct. Indeed, the calculation of clearance indicated a value lower than that quoted by McNeil and Louis (1984). Thus, with this calculated value of clearance, the infusion rate required to maintain a C^{ss} of 170 ng ml^{-1} would appear to be 0.13 mg

$kg^{-1}\,h^{-1}$. Dagnino and Prys-Roberts (1985) demonstrated that, in patients presented for aortic replacement surgery, an infusion rate of 0.15 mg $kg^{-1}\,h^{-1}$ produced a significant decrease in the response to isoproterenol; the chronotropic dose 25 was 95 µg. In our patients, this C^{ss} was obtained in the absence of bradycardia, hypotension or myocardial failure as shown by haemodynamic stability during the infusion. This fact may be explained by the high degree of resting sympathetic drive inducing tachycardia and hypertension during the control period. We advocate that the infusion be started at a lower rate (between 0.07 and 0.15 mg $kg^{-1}\,min^{-1}$) and be increased only if hypertension and tachycardia are still present. A lower infusion rate is especially necessary in patients with poorly documented or altered left ventricular function or abnormal liver function.

In contrast to other reports (Richards et al., 1977; McNeil and Louis, 1984) we did not observe any correlation between plasma concentrations and changes in HR or MAP. The main reasons are the dose, which was the same for all patients and induced the same degree of haemodynamic change, and the lack of any quantitation of the degree of β-adrenoreceptor blockade with the isoproterenol dose–response (Dagnino and Prys-Roberts, 1985).

It is concluded that labetalol is a very effective antihypertensive agent during the postoperative period. The hypotensive effect is produced mainly by a decrease in CO caused by a decrease in HR without increasing SVR. This clearly contrasts with the effect of pure β-adrenoreceptor blocking agents. Although labetalol neither significantly decreased mean SI nor increased ventricular filling pressures, it had a negative inotropic effect which necessitated normal ventricular function for the doses used in the present series. The method of administration used in this study, combining a loading dose and a constant infusion, offers the potential for a rapid and stable haemodynamic effect, but the calculation of the infusion rate must be based on a clearance of 13 ml $kg^{-1}\,min^{-1}$.

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HIGH FREQUENCY JET VENTILATION: THE INFLUENCE OF DIFFFERENT METHODS OF INJECTION ON RESPIRATORY PARAMETERS†

D. BENHAMOU, C. ECOFFEY, J. J. ROUBY, C. SPIELVOGEL AND P. VIARS

SUMMARY

Fourteen critically ill patients with ventilatory failure were ventilated with HFJV using a constant driving pressure of 3 atm and a constant I:E ratio of 0.43. In six (group I) HFJV, using a frequency of 100 b.p.m., was delivered via a proximal injector cannula. Four injector cannulae (i.d. 1.8, 1.6, 1.4 and 1.2 mm, respectively) were used at random. In eight patients (group II), HFJV using three frequencies (100, 300 and 600 b.p.m.) was administered either via a 1.8-mm i.d. proximal injector cannula (proximal injection), or via a Hi-Lo jet tracheal tube (distal injection). The following indices were measured in vivo*: mean airway pressure ($P_{\overline{aw}}$), mean pulmonary volume above apnoeic FRC ($\Delta\bar{V}$), mean alveolar pressure (clamps method) and arterial blood-gas tensions. Injected volume (Vinj), entrainment (E) and tidal volume (VT) were measured* in vitro *using a water-sealed spirometer. Operating pressure (the pressure in the connecting tube) was measured directly using a high pressure calibrated transducer. In group I, $P_{\overline{aw}}$, $\Delta\bar{V}$, Pa_{O_2}, Vinj and VT significantly decreased whereas operating pressure and E significantly increased when the internal diameter of the injector cannula was reduced. In group II, $P_{\overline{aw}}$, $\Delta\bar{V}$, E, VT and operating pressure significantly decreased, whereas Vinj increased and Pa_{O_2} and Pa_{CO_2} remained unchanged, when proximal injection was switched to distal injection. In both groups, a significant relationship was found between operating pressure and E. At a constant driving pressure, operating pressure increased with narrow injector cannulae and increased frequency, and decreased when proximal injection was switched for distal injection.*

Many experimental and clinical studies have attempted to define the physiological principles and potential clinical applications of High-Frequency Jet Ventilation (HFJV). However, the basic knowledge on the technical aspects of this new mode of ventilation remains confusing because of a lack of uniformity in equipment. For example, the exact role of the physical characteristics of the system of injection have been poorly documented. Previous studies, undertaken to determine the respiratory effects of changing the internal diameter of classical proximal injector cannulae, have yielded conflicting results (Bluth, Banner and Gallagher, 1980; Carlon et al., 1983). Recently, several studies have been published on high frequency ventilation administered via specially constructed jet tracheal tubes (Davey, Lay and Laigh, 1982; Otto et al., 1983; Benhamou, Bourgain et al., 1984; Rossing et al., 1984). These jet tracheal tubes, having a jet insufflation channel embedded into their side wall, enable distal injection close to the carina. They have gained wide popularity among clinicians and nurses because they enable tracheal suction without disconnection of the patient from the ventilator. However, there has been no comparative study between the classical proximal injection and this new "distal injection". Therefore, we undertook a prospective study in critically ill patients receiving HFJV for acute ventilatory failure to investigate the respiratory changes

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D. BENHAMOU, M.D.; C. ECOFFEY, M.D.; J. J. ROUBY, M.D.; C. SPIELVOGEL, M.D.; P. VIARS, M.D.; Département d'Anesthésie-Réanimation, Centre Hospitalo-Universitaire Pitié-Salpétrière 83 Boulevard de l'Hôpital, 75651 Paris Cedex 13, France. Accepted for Publication: August 4, 1986.

Correspondence to J. J. R.

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TABLE I. *Clinical status of the patients before the study under intermittent positive pressure ventilation. *Static thoraco-pulmonary compliance was measured using a 2-litre syringe and the pressure–volume curve was directly recorded on an X–Y 2000 Omnigraphic Houston Instrument (Rouby et al., 1985)*

Patient	Sex	Age (yr)	Clinical diagnosis	Static thoraco-pulmonary compliance (ml/cm H_2O)*	Pa_{O_2} (FI_{O_2} = 1) (kPa)	Pa_{CO_2} (kPa)
Group I						
1	M	30	Bacterial pneumonia	25	34	3.7
2	M	18	Cerebral contusion	84	32	4.3
3	F	40	Multiple trauma	60	32	3.3
4	F	62	Peritonitis	52	37	4.4
5	F	75	Multiple trauma	65	42	3.9
6	M	43	Multiple trauma	72	31	4.3
Group II						
1	M	76	Herpetic encephalitis	108	36	3.1
2	F	76	Acute pancreatitis	63	16	4.7
3	M	70	Postoperative ventilatory failure	96	21	3.7
4	F	63	Postoperative ventilatory failure	57	36	4.0
5	F	76	Multiple trauma	68	43	4.3
6	M	72	Multiple trauma	95	30.1	4.3
7	M	41	Postoperative ventilatory failure	54	39	4.4
8	M	39	Bacterial pneumonia	105	53	4.9

induced by modifying the internal diameter of the classical proximal injector cannula, and to compare proximal and distal injections.

PATIENTS AND METHODS

Patients

Fourteen patients admitted to the Surgical Intensive Care Unit of La Pitié Hospital were selected according to the following criteria:

(1) Ventilatory failure necessitating conventional mechanical ventilation;

(2) stable haemodynamic condition without evident hypovolaemia;

(3) presence of radial artery catheter as an integral part of cardiovascular monitoring;

(4) absence of chronic obstructive pulmonary disease or asthma.

All patients were ventilated initially using a CPU 1 ventilator (Ohmeda Maurepas, France) with a tidal volume of 10–12 ml kg^{-1}, a frequency of 15 b.p.m. and an I:E ratio of 0.43. Patients were divided into two groups. Six patients in whom the trachea was intubated or in whom tracheotomy had been performed, received HFJV via a classical proximal injection using four injector cannulae differing only by their internal diameter. Eight were intubated with a Hi-Lo jet tracheal tube and received HFJV either via a classical proximal injector cannula or via the jet insufflation channel of the tube (distal injection). To avoid spontaneous breathing, pancuronium bromide 0.1 mg kg^{-1} was added to a continuous infusion of fentanyl 40 µg kg^{-1} day^{-1}. Informed consent was obtained from each patient's legal guardian and authorization was given by the Clinical Investigation Committee of this Institution. The initial individual clinical status of each patient under intermittent positive pressure ventilation is summarized in table I.

Equipment (fig. 1)

HFJV was administered using a jet ventilator MK 800 (Acutronic Medical Systems AG Switzerland) throughout the duration of the study and conventional positive pressure ventilation was used as prolonged ventilatory support throughout the course of the respiratory disease. The HFJV circuit has been described previously (Rouby et al., 1983) and only the most important details are presented. Air and oxygen were supplied to the ventilator under a constant pressure of 3 atm. The electronically controlled solenoid valve had an internal diameter of 2.2 mm. The jet ventilator was connected to the patient via a connecting tube (i.d. 7 mm, length 65 cm) having a compliance of 0.022 ml/cm H_2O. Since all circuits had internal diameters greater than 2.2 mm, flows and press-

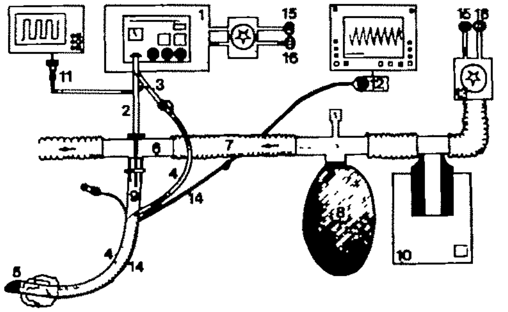

FIG. 1. Circuit for HFJV. 1 = Ventilator MK 800; 2 = connecting tube in proximal injection; 3 = connecting tube in distal injection; 4 = Jet insufflation channel; 5 = Hi-Lo jet tracheal tube; 6 = three-way swivel adaptor; 7 = bias flow for entrained gases; 8 = anaesthesia bag; 9 = injector cannula; 10 = heater-humidifier; 11 = high pressure calibrated transducer for measuring operating pressure; 12 = low pressure calibrated transducer for measuring P_{aw}; 13(☆) = blenders; 14 = airway pressure monitoring channel; 15 = air; 16 = oxygen.

ures in the circuits were mainly determined by the length and the internal diameter of the injection system. The connecting tube was connected either to a classical injector cannula (length 55 mm, i.d. 1.2, 1.4, 1.6, or 1.8 mm) fixed to the proximal tip of a conventional tracheal or tracheostomy tube via a three-way swivel adaptor, or to the jet insufflation channel (length 390 mm, i.d. 2 mm) of a Hi-Lo jet tracheal tube (NCC Division Mallinckrodt Inc., Argyl N4). In both types of injection, gas for entrainment was provided by an open anaesthetic breathing system delivering warmed and humidified gases (30 litre min^{-1}) at the same $F\text{I}_{O_2}$ as the gases delivered by the ventilator. Throughout the study, driving pressure—that is, the pressure before the solenoid valve—was maintained constant at 3 atm and I:E ratio was set at 0.43.

Measurement of intrathoracic pressures and pulmonary volumes

In the case of proximal injection, mean airway pressure (P_{aw}) was measured using a polyethylene catheter advanced into the tracheal tube 10 cm beyond the distal tip of the injector cannula. In the case of distal injection, P_{aw} was measured using the second auxiliary channel (i.d. 1 mm) of the Hi-Lo jet tracheal tube. This channel ends 1 cm above the distal tip of the tracheal tube, whereas the jet insufflation channel ends 6 cm above the distal tip of the tracheal tube. Consequently, airway pressure was measured 5 cm below the outlet of the jet insufflation channel. In a preliminary study, we verified the accurary of measuring P_{aw} through this channel (Brichant, Rouby and Viars, 1986). A catheter ending 10 cm below the outlet of the jet insufflation channel was introduced to the trachea and P_{aw} measured from this catheter was compared with P_{aw} measured from the airway pressure monitoring channel of the Hi-Lo jet tracheal tube, in five consecutive patients. In each individual, the difference between the two measurements never exceeded 1 mm Hg. Therefore, the airway pressure monitoring channel of the Hi-Lo jet tracheal tube was considered adequate for measuring P_{aw}. In both types of injection, the entire measuring system (polyethylene catheter or airway pressure monitoring channel + air-filled connector + low pressure calibrated quartz transducer 1290 A (Hewlett-Packard)) had a resonant frequency of 3 Hz and consequently, P_{aw} only, obtained by electronic damping of the signal, will be reported. Mean alveolar pressure and mean pulmonary volume above apnoeic FRC ($\Delta\bar{V}$) were measured as follows. The ventilator was stopped and the connecting tube and the expiratory circuit were clamped simultaneously for a few seconds; this stopped all flow and enabled pressures throughout the lung to become equal at a value close to the mean alveolar pressure. The expiratory line was then connected to a calibrated water-sealed spirometer and $\Delta\bar{V}$ was measured by declamping the expiratory line. Four consecutive measurements were made to minimize the margin of error from the application of the clamps at different phases of the ventilatory cycle. For a given ventilatory setting, the greatest difference between the five measurements never exceeded 250 ml for $\Delta\bar{V}$ and 0.13 kPa (1 mm Hg) for mean alveolar pressure.

Measurement of operating pressure, injected volume, gas entrainment and tidal volume

Operating pressure—that is, the pressure between the solenoid valve and the injection system—was measured in the connecting tube using a high pressure calibrated transducer (Schlumberger CZ 9029, linear in the range 0–5 atm, resonant frequency 150 Hz). The quality of the electrical signal was improved by a conditioning amplifier (Thompson) connected online to a storage oscilloscope (Textronix 5223). The signal displayed on the screen was finally reproduced at 500 mm s^{-1} on an X–Y recorder (Sefran TGV 164).

Injected volume (Vinj)—the jet volume de-

TABLE II. *Effects of changing the internal diameter of the injector cannula in group I* (n = *6, mean values* ± *SD*). *P < *0.05* v. *1.8 mm*

	Injector cannula size (mm)			
	1.8	1 6	1.4	1.2
In vivo				
P_{IW} (kPa)	2.3±0.3	2.0±0.3*	1.8±0.2*	1.7±0.3*
Mean alveolar pressure (kPa)	2.3±0.3	2.1±0.2*	1.8±0.3*	1.7±0.3*
$\Delta\bar{V}$ (ml)	1399±516	1255±487*	1028±447*	892±473*
Operating pressure (atm)	2	2.2*	2.4*	2.6*
In vitro				
E (%)	60±3.7	63.5±40*	69±7*	70±3*
*V*inj (ml)	136±5	106±12*	81±16*	73±8*
*V*T (ml)	339±30	290±9*	257±21*	243±5*

livered by the ventilator—and entrainment were measured *in vitro* as follows: HFJV was stopped, disconnected from the patient, and the lateral openings of the three-way swivel adaptor obstructed to avoid any entrainment. The jet ventilator was then connected to a tracheal tube identical to that attached to the patient, itself connected in an air-tight manner to the inspiratory line of a previously calibrated water-sealed spirometer of which the expiratory line had been clamped. For each type of injection, HFJV was started and recordings of *V*inj were made at a speed of 25 mm s^{-1} to separate the different phases of the ventilatory cycle. At the end of the inspiration time, *V*inj was considered to be entirely delivered. Three consecutive measurements were made. Tidal volume was then measured as follows: the two lateral openings of the three-way swivel adaptor were opened and connected to inspiratory and expiratory lines of the additional gas circuit. Tidal volume (*V*T), resulting from the addition of the entrained volume to *V*inj, was then measured in triplicate. It was thus possible to calculate entrainment fraction (*E*%):

$$E\% = \frac{V\text{T} - V\text{inj}}{V\text{T}}$$

It must be pointed out that these *in vitro* measurements only gave some idea of the direction of variation of *E* and *V*T and cannot be considered as the true *E* and *V*T delivered to the patients. Since *E* is dependent on operating pressure (Benhamou, Ecoffey et al., 1984) and on airway resistance (Bourgain et al., 1983), it is clear that *E* and *V*T, measured *in vitro* using a water-sealed spirometer having a low internal resistance, were overestimated compared with *V*T and *E* administered *in vivo*. In fact, these *in vitro* measurements provide useful information concerning the effects of changing either the operating pressure or the physical characteristics of the injection system, independent of changes in the patient's airway resistance. Since patients with chronic obstructive pulmonary disease and asthma were excluded from the study, it is likely that the direction of variation of *E* and *V*T were identical between *in vivo* and *in vitro* conditions, although absolute values were certainly different. On the other hand, it has been demonstrated that *V*inj is independent of airway resistance and ventilatory compliance, at least when the Acutronic Jet Ventilator is used (Bourgain et al., 1983). Consequently, our *in vitro* measurements can be considered as adequate for measuring *V*inj.

Procedures

The effects of changing the internal diameter of the proximal injection were studied in six patients (group I). Four injector cannulae of various internal diameters (1.2, 1.4, 1.6 and 1.8 mm) were used at random in each patient with identical ventilatory settings: frequency 100 b.p.m., I:E ratio 0.43 and driving pressure 3 atm.

The effects of switching proximal injection to distal injection were studied in eight patients (group II). Proximal injection using a 1.8-mm i.d. injector cannula, and distal injection, using the Hi-Lo jet tracheal tube, were used at random in each patient. Driving pressure and I:E ratio were maintained constant at 3 atm and 0.43, respectively, and three frequencies were used: 100, 300 and 600 b.p.m.

For each type of injection and each ventilatory setting, operating pressure, P_{IW}, mean alveolar pressure, $\Delta\bar{V}$, Pa_{O_2} and Pa_{CO_2} were measured

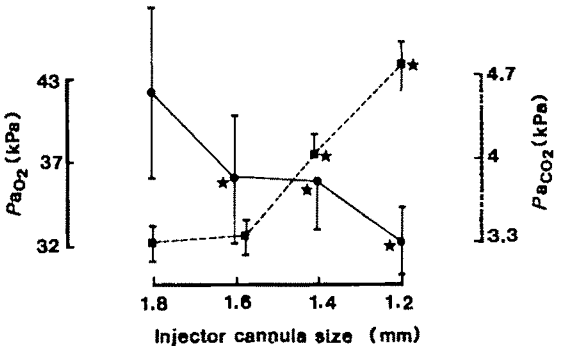

FIG. 2. Effects of increasing the internal diameter of the injector cannula on Pa_{O_2} ($FI_{O_2} = 1$) (●——●) and Pa_{CO_2} (■---■) in group I ($n = 6$). $^*P < 0.05$ compared with 1.8-mm injector cannula.

in vivo after a steady state of 20 min at FI_{O_2} 1. *V*inj, *V*T and *E* were then measured *in vitro*.

Statistical analysis

All data are presented as mean ± SD. In group I, a two-way analysis of variance complemented by a modified *t* test was used to compare the effects of changing the internal diameter of the injector cannula. In group II, a two-way analysis of variance complemented by a modified *t* test was used to compare the effects of increasing frequency. Since the number of subjects was small and normal distribution for the data could not be ensured, we used a non-parametric Wilcoxon signed rank test to compare distal and proximal injections at a given frequency. Relationships between operating pressure and *E* were determined by linear regression analysis using the method of least squares.

RESULTS

Decreasing the internal diameter of the injector cannula induced significant decreases in P_{SW}, mean alveolar pressure and $\Delta\bar{V}$ (table II). These changes were paralleled by a significant decrease in Pa_{O_2} and a significant increase in Pa_{CO_2} (fig. 2). *V*inj and *V*T decreased significantly, whereas operating pressure and *E* increased significantly.

For a given ventilatory frequency, switching proximal injection to distal injection induced significant decreases in P_{SW}, mean alveolar pressure, $\Delta\bar{V}$, *E*, *V*T and operating pressure, whereas Pa_{O_2} and Pa_{CO_2} remained unchanged and *V*inj increased (table III).

For a given type of injection, increasing ventilatory frequency induced significant decreases in *E*, *V*inj, *V*T and operating pressure, whereas P_{SW}, mean alveolar pressure $\Delta\bar{V}$ and Pa_{O_2} remained unchanged. These changes were paralleled by a significant increase in Pa_{CO_2} (table III).

The reason why operating pressure increased with ventilatory frequency despite a constant driving pressure of 3 atm, is clearly shown in figure 3. According to the physical characteristics of the connecting tube, the duration required to reach the maximum value of the operating pressure was 0.1 s. At 100 b.p.m., with an I:E ratio of 0.43, the inspiratory time allotted to the ventilatory settings was around 0.2 s. Consequently, operating pressure could reach its

TABLE III. *Comparative effects of proximal and distal injections at three different ventilatory frequencies in group II* (n = 8, *mean values* ± *SD*). *P < *0.05 proximal* v. *distal*; †P < *0.05* v. *100 b.p.m.*

	Ventilatory frequency (b.p.m.)					
	100		300		600	
	Proximal	Distal	Proximal	Distal	Proximal	Distal
In vivo						
P_{SW} (kPa)	2.3* ± 0.71	1.5 ± 0.52	2.3* ± 0.71	1.5 ± 0.45	2.2* ± 0.84	1.3 ± 0.8
Mean alveolar pressure (kPa)	2.1* ± 0.68	1.4 ± 0.45	2.2* ± 0.65	1.4 ± 0.45	2.1* ± 0.73	1.1 ± 0.45
$\Delta\bar{V}$ (ml)	1707* ± 676	1302 ± 568	1722* ± 603	1172 ± 580	1641* ± 964	1034 ± 827
Pa_{O_2} (kPa)	38 ± 9	42 ± 9	43 ± 9	38 ± 9	40 ± 8	39 ± 9
Pa_{CO_2} (kPa)	3.3 ± 0.8	3.6 ± 0.53	5.2† ± 1.5	5.5† ± 1.5	7.3† ± 1.6	7.7† ± 1.5
Operating pressure (atm)	2	1.8*	1.8†	1.3*†	1.6†	1.2*†
In vitro						
E (%)	59 ± 3.5	41* ± 7	38† ± 3	25*† ± 2.5	25† ± 2	17*† ± 3
*V*inj (ml)	145 ± 8.4	162* ± 10	50† ± 2.1	60*† ± 1.8	45† ± 1.4	50*† ± 1.6
*V*T (ml)	353 ± 23	277* ± 19	80† ± 3.6	70*† ± 2.6	60† ± 1.7	60*† ± 1.7

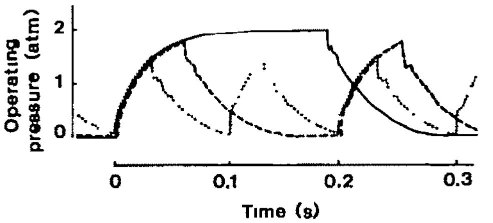

FIG. 3. Changes in operating pressure induced by increasing frequency (—— = 100 b.p.m.; --- = 300 b.p.m.; .... = 600 b.p.m.). Operating pressure (the pressure inside the connecting tube) was measured directly using a high pressure calibrated transducer and the signal was improved by a conditioning amplifier connected on-line to a storage oscilloscope (see Methods). For each trace, driving pressure = 3 atm and I:E = 0.43.

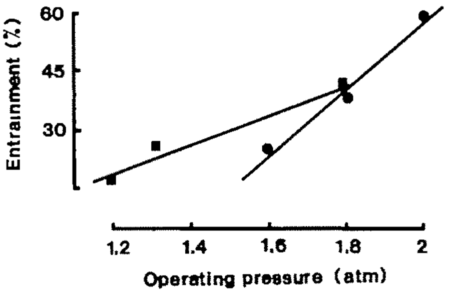

FIG. 4. Relationship between entrainment and operating pressure in group II ($n = 8$). ● = Proximal injection; ■ = distal injection.

maximum inspiratory value (that is, the driving pressure, 3 atm, minus the pressure loss in the blender, 1 atm). At 300 b.p.m. inspiratory time allotted to the ventilatory settings decreased to 0.09 s and, consequently, expiration occurred before the operating pressure had reached its maximum value, 2 atm. At 600 b.p.m., inspiratory time allotted to the ventilatory settings further decreased to 0.04 s and, consequently, the end-inspiratory value of the operating pressure decreased in parallel.

In both groups, a significant relationship was found between operating pressure and *E*. In group I, changes in operating pressure were induced by changing the internal diameter of the injector cannula; the regression equation was $y = 18.1x + 24$ ($r = 0.66$; $P < 0.01$), where y = entrainment and x = operating pressure. In group II, changes in operating pressure were induced by increasing frequency, and the regression equation, in the case of proximal injection, was $y = 85x - 112$ ($r = 0.09$; $P < 0.01$). The regression equation in the case of distal injection was $y = 37x - 26$, ($r = 0.99$; $P < 0.01$) (fig. 4). This latter result clearly indicates that distal injection alone decreases *E*.

DISCUSSION

This study demonstrates that using injector cannulae of decreasing internal diameter during HFJV leads to a marked decrease in PEEP effect, and to a significant reduction in alveolar ventilation. During HFJV, flow and, consequently, *V*inj are determined by the source pressure (operating pressure) and by the sum of the resistances of the different components of the circuit. Since the solenoid valve of the Acutronic jet ventilator has a diameter of 2 mm, and all the injector cannulae tested in the study were smaller than this, *V*inj was determined mainly by the operating pressure and diameter of the injector cannula. Since driving pressure was maintained constant at 3 atm, it is not surprising that a decrease in *V*inj and an increase in operating pressure were found when using injector cannulae of decreasing internal diameter. *In vitro*, we found that an increase in operating pressure was associated with an increase in *E*, not sufficient, however, to avoid a marked decrease in *V*T. Since our volume measurements *in vitro* overestimated *E* and, consequently, *V*T, the true *V*T administered to the patients were probably smaller. Because carbon dioxide elimination in HFJV is inversely related to the absolute value of *V*T (Rouby et al., 1985), a marked increase in Pa_{CO_2} was observed when using narrow injector cannulae. It was also recently demonstrated that a decrease in *V*T with no modification in expiratory time, will shorten spontaneous lung relaxation time and, consequently, decrease HFJV-induced "PEEP effect" (Rouby et al., 1985). This phenomenon, initially observed with decreasing driving pressure, was possibly involved in the decrease in $\Delta\bar{V}$, P_{aw} and Pa_{O_2} induced by decreasing the internal diameter of the injector cannula. It is obvious that identical results—decrease in *V*T and reduction in lung distension—could have been observed also by increasing the length of the injector cannula without modifying the internal diameter. Such a method of injection, widely used for vocal cord surgery (Eurin et al., 1983), will then require higher driving pressures in order to limit the reduction in *V*T. Finally, the use of small injector cannulae during HFJV, could be appealing in paediatrics, since *V*T values required to achieve an adequate carbon dioxide elimination are much smaller in infants than in adults.

When proximal injection was switched to distal injection, a significant reduction in lung distension was observed without any significant change in Pa_{CO_2}. In other words, distal injection enabled the same carbon dioxide elimination at a decreased P_{aw}. VT, measured *in vitro*, decreased significantly, mainly because of a marked reduction in E. Several factors contributed to the decrease in E in distal injection. First, operating pressure was reduced because the internal diameter of the jet insufflation channel of the Hi-Lo tracheal tube was greater than the internal diameter of the injector cannula (2 mm *v.* 1.8 mm). Second, the distal tip of the jet insufflation channel is far removed from the bias flow and, consequently, the kinetic energy required to entrain the already moving gas of the cross-flow towards the distal airways in proximal injection is presumably lower than that necessary to entrain tracheal tube immobile gas in distal injection. Third, the lateral site of injection during distal injection is much less efficient for E than is the co-axial site of injection during proximal injection. This is clearly illustrated by figure 4 which shows that, for a given increase in operating pressure, the corresponding increase in E is greater in proximal injection than in distal injection. For all these reasons, and despite a greater Vinj in distal injection, E was so reduced that VT constantly decreased when proximal injection was switched to distal injection. Since *in vitro* measurements tend to overestimate VT and E, it is likely that decreased VT and E were more marked *in vivo*. Therefore, since expiratory time remained unchanged, the decrease in VT resulted in marked decreases in $\Delta \bar{V}$, P_{aw} and mean alveolar pressure. Surprisingly, this decrease in VT was associated with an unchanged Pa_{CO_2}. Since other patients were stable haemodynamically and clinically during the study, and were heavily sedated by large doses of fentanyl, it can be assumed that variations in Pa_{CO_2} reflected changes in carbon dioxide clearance rather than variations in its production. Consequently, unchanged Pa_{CO_2} associated with markedly reduced VT clearly suggest that distal injection was associated with a reduction in anatomical deadspace. It is likely also that, if identical VT had been applied in proximal and distal injections, lung distension would have been identical, but Pa_{CO_2} significantly lower in distal injection. Finally, the major advantage of distal injection over proximal injection is the decrease in anatomical deadspace obtained by injecting closer to the carina (Davey, Lay and Laigh, 1982). This enables an improvement in carbon dioxide elimination associated with a decrease in intrathoracic pressure. Moreover, the simplicity of the method, the possibility of suctioning without disconnecting the patient from the ventilator, the security and the flexibility of the connection between the patient and the ventilator and the easy monitoring of P_{aw}, makes the distal injection through a Hi-Lo jet tracheal tube the method of choice for administering HFJV to critically ill patients.

Another important finding of this study was that operating pressure, which is not commonly monitored during HFJV, was dependent not only on driving pressure, but also on frequency and type of injection. Operating pressure influences HFJV-induced lung distension and carbon dioxide elimination (Benhamou, Ecoffey et al., 1984) through its effects on E (Rouby et al., 1985). The greater the operating pressure, the greater the value of E (fig. 4). Moreover, an important part of the respiratory effects allotted to a given type of injection, are in fact dependent on simultaneous variations in operating pressure, the driving pressure remaining constant.

For example, Vinj was greater in distal than in proximal injection, although VT and lung distension were smaller. This was in part the result of the fact that operating pressure significantly decreased in distal injection which, in turn, reduced E and, finally, VT. This effect was emphasized by the lateral site of injection which also contributed to the decrease in E. Consequently, a good part of the respiratory effects of distal injection were related to changes in operating pressure and not to the jet injection system itself.

In fact, the connecting tube acts as an RC system interposed between the ventilator and the injector cannula. Each time inspiratory time allotted to the ventilatory settings is less than the time necessary for the pressure to reach its maximum inspiratory value, operating pressure decreases.

This is illustrated in figure 4, which shows the effects of increasing frequency on operating pressure: operating pressure decreases as inspiratory time is reduced. It is clear that the physical properties of the connecting tube greatly influence this effect. Bringing the solenoid valve closer to the injector cannula through a short rigid connecting tube would be ideal in limiting changes in operating pressure as a result of changes in inspiratory time, but is obviously difficult to realize in clinical practice. However, the relationship between driving pressure and operating pressure is a key factor in the quality of a jet ventilator. Further improvements in technology should focus on this point.

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EFFECTS OF EXTRADURAL ANAESTHESIA ON HUMAN FETAL BLOOD FLOW *IN UTERO*

Comparison of Three Local Anaesthetic Solutions

A. LINDBLAD, J. BERNOW, E. VERNERSSON AND K. MARSÁL

SUMMARY

Twenty-seven women, scheduled for elective Caesarean section under extradural anaesthesia were allocated randomly to one of three groups: group Ea received 1.5% etidocaine with adrenaline, group Bp 0.5% bupivacaine plain, and group Ba 0.5% bupivacaine with adrenaline. There was no difference in the quality and distribution of sensory blockade between the three groups. Motor blockade was most profound in group Ea. Maternal heart rate and arterial pressure were only slightly affected in the three groups. Before induction of extradural anaesthesia, and 15 and 30 min after, fetal umbilical and aortic blood flows were examined using a combination of real-time ultrasonography and the pulsed Doppler technique. Blood flow in the umbilical vein was not affected in any of the groups, and blood flow in the fetal aorta remained unchanged in groups Ea and Bp, but was increased by 12% after 30 min in group Ba. We conclude that, with the three local anaesthetic solutions studied during extradural anaesthesia for elective Caesarean section, fetal circulatory variables remained stable and within normal limits, when in association with normal values of maternal arterial pressure.

The administration of extradural anaesthesia to patients undergoing elective Caesarean section allows the mother to be awake, minimizes the risk of pulmonary aspiration and avoids the depressant effects of general anaesthetics on the neonate (Shnider and Levinson, 1974). In our department, 60% of all elective Caesarean sections were performed under extradural anaesthesia during 1986. However, there is a possibility that the technique could cause arterial hypotension in the mother, with a consequent impairment of uterine blood flow and placental perfusion—and this may, in turn, affect the circulation of the fetus. Direct effects of the local anaesthetic on fetal circulation are unlikely, provided conventional doses are used and inadvertent intravascular injection is avoided.

Until recently, it was not possible to study the human fetal circulation other than by cardiotocography. However, recent advances in ultrasonography have made it possible to investigate the fetal circulation *in utero* (Eik-Nes, Brubakk and Ulstein, 1980). In a preliminary study of extradural anaesthesia in conjunction with Caesarean section in six patients, 1.5% etidocaine was combined with 0.5% bupivacaine, both containing adrenaline at 5 $\mu g\ ml^{-1}$, and we were able to show that there was no effect on the fetal circulation (Lindblad et al., 1984). The purpose of the present study was to evaluate the effects, on the fetal circulation, of extradural anaesthesia with three commonly-used local anaesthetic solutions, and to confirm the results of the preliminary study.

PATIENTS AND METHODS

Twenty-seven women scheduled for elective Caesarean section participated in the study, which was approved by the Ethics Committee of the Medical Faculty, University of Lund, informed consent being obtained from all women. They all had uncomplicated pregnancies. Data on maternal age, weight, height, parity, gestational age and neonatal birthweight are summarized in table I.

ANNIKA LINDBLAD, M.D., KAREL MARSÁL, M.D., PH.D. (Department of Obstetrics and Gynecology); JENS BERNOW, M.D., EINAR VERNERSSON, M.D. (Department of Anaesthesia); Malmo General Hospital, S-214 Malmo, Sweden. Accepted for Publication: December 24, 1986.

Correspondence to A.L.

TABLE I. *Clinical characteristics of women and newborns. Ea = 1.5% Etidocaine with adrenaline; Bp = 0.5% bupivacaine; Ba = 0.5% bupivacaine with adrenaline*

		Group Ea ($n = 9$)	Group Bp ($n = 9$)	Group Ba ($n = 9$)
Women				
Age (yr)	Mean	32.7	29.9	32.8
	SD	6.3	6.5	4.3
Weight (kg)	Mean	69.2	66.6	65.7
	SD	7.4	3.8	8.6
Height (cm)	Mean	164.0	156.3	158.1
	SD	5.1	8.5	6.5
Parity (primiparae/multiparae)		5/4	3/6	3/6
Newborns				
Gestational age (weeks)	Mean	38.7	38.7	38.5
	SD	1.4	0.7	0.7
Birthweight (g)	Mean	3628	3336	3172
	SD	257	462	322

The indications for Caesarean section are listed in table II.

The three local anaesthetic solutions used were administered in random fashion; apart from the anaesthetist, the investigators were blind to the particular solution administered. The women were divided into three groups: group Ea ($n = 9$) received extradural anaesthesia with 1.5% etidocaine with adrenaline 5 μg ml^{-1}, group Bp ($n = 9$) 0.5% bupivacaine plain and group Ba ($n = 9$) 0.5% bupivacaine with adrenaline 5 μg ml^{-1}.

Premedication with atropine 0.25 mg i.v. was given to three, four and four women in groups Ea, Bp and Ba, respectively, just before the induction of anaesthesia. The remaining patients received no premedication. After the infusion of 500–1000 ml of a balanced electrolyte solution, an extradural catheter was introduced through a 16-gauge needle at the L3–4 ($n = 20$) or the L2–3 ($n = 7$) space with the woman in the sitting position. A test dose of 4 ml of local anaesthetic was given to exclude subarachnoid or i.v. administration. The total dose was determined according to the height of the patient by means of a schedule used at our department (table III). Half of the remaining dose was given 4 min after the test dose, with the woman still sitting. After another 5 min, the woman was placed supine, tilted 45 ° to the right side, and given the rest of the total dose. This point was defined as time zero. At +5 min, the woman was turned to a 15 ° left-tilted position, and a further 1 litre of balanced electrolyte solution was given. Maternal heart rate (ECG) was recorded continuously. Maternal arterial pressure was recorded by auscultation before the induction of extradural anaesthesia, and every 2–3 min thereafter, until the start of the operation, during which it was recorded every 5 min. Ephedrine 5–10 mg i.v. was given if a reduction in systolic arterial pressure indicated imminent hypotension (< 90 mm Hg).

The distribution of cutaneous analgesia was

TABLE II. *Indications for the elective Caesarean section. Ea = 1.5% etidocaine with adrenaline; Bp = 0.5% bupivacaine; Ba = 0.5% bupivacaine with adrenaline*

	Group Ea ($n = 9$)	Group Bp ($n = 9$)	Group Ba ($n = 9$)
Cephalopelvic disproportion	3	6	5
Breech presentation and borderline pelvis	4	3	3
Other indications	2	0	1

TABLE III. *Total extradural dose of the local anaesthetics*

Maternal height (cm)	1.5% Etidocaine with adrenaline (ml)	0.5% Bupivacaine plain or with adrenaline (ml)
130–139	12	18
140–149	14	20
150–159	16	22
160–169	18	24
170–179	20	26

TABLE IV. *Segmental spread of analgesia 15 and 30 min after induction of the extradural blockade. Ea = 1.5% etidocaine with adrenaline; Bp = 0.5% bupivacaine; Ba = 0.5% bupivacaine with adrenaline. T = Thoracic dermatome*

		Group Ea ($n = 9$)	Group Bp ($n = 9$)	Group Ba ($n = 9$)
15 min	Median	T7	T8	T8
	Range	T1–T10	T6–T10	T6–T10
30 min	Median	T5	T5	T5
	Range	T1–T9	T2–T6	T3–T8

recorded 15 and 30 min after the induction of extradural anaesthesia (table IV). After the completion of the blood flow measurements, an additional dose of the local anaesthetic solution (25% of the total dose according to table III) was given to obtain a cephalic spread to T5. Using Bromage's scale (1965), the degree of motor blockade was recorded just before the start of surgery. Sensory blockade was assessed, during surgery, on a scale from 1 to 4, where 1 represented excellent analgesia, 2 mild discomfort requiring supplementary analgesia after delivery, 3 discomfort requiring supplementary analgesia before delivery, and 4 inadequate sensory block—general anaesthesia required. If the woman felt pain before delivery, 50% nitrous oxide in oxygen was administered, and if she felt discomfort after delivery, pethidine was given. Two days after surgery, each woman was asked to comment on her experience, and to state whether or not she would prefer a Caesarean section under extradural anaesthesia on a future occasion. At the same time, any late complications caused by the anaesthetic procedure were recorded.

Before the induction of extradural anaesthesia, and 15 and 30 min thereafter, fetal heart rate and fetal blood flow were recorded. Fetal heart rate was counted from the blood velocity tracings. Blood flow was recorded from the thoracic part of the fetal descending aorta and from the intra-abdominal part of the umbilical vein, and measured using the ultrasound method described by Eik-Nes, Marsál and Kristoffersen (1984), combining a real-time linear array scanner (ADR, Model 2130, Advanced Diagnostic Research Corporation, Tempe, Arizona; 3.5 MHz) and a pulsed Doppler instrument (Alfred, Vingmed A/S, Oslo, Norway; 2.0 MHz). A 100-Hz high-pass filter of the Doppler signal was used. The Doppler transducer was attached to the real-time transducer at a fixed angle of 45 °, thus enabling correction of the recorded blood velocity for the angle. The calculations of blood velocity (V) for each measurement were made on Doppler traces of at least 10 s duration obtained under steady state conditions without fetal breathing or gross movement. Vessel cross-sectional area (A), assumed to be circular, was calculated from the mean value of 10 vessel diameters measured in 10 frozen real-time images. The blood flow (Q) was calculated according to the formula $Q = V.A/\cos 45°$. The blood flow was related to the infant's birthweight and expressed in ml min^{-1} kg^{-1}. The waveform of the maximum velocity curves recorded from the fetal aorta was analysed by computer (ABC 806, Luxor, Motala, Sweden), and characterized by the following variables: peak velocity (V_{peak}), pulsatility index (PI) and rising slope (RS) (fig. 1) (Lingman and Marsál, 1986). PI indicates changes in vascular resistance peripheral to the site of measurement (Gosling et al., 1971), and RS reflects myocardial contractility (Marsál et al., 1985). The ultrasound intensities used were within recommended limits (Lingman, 1985).

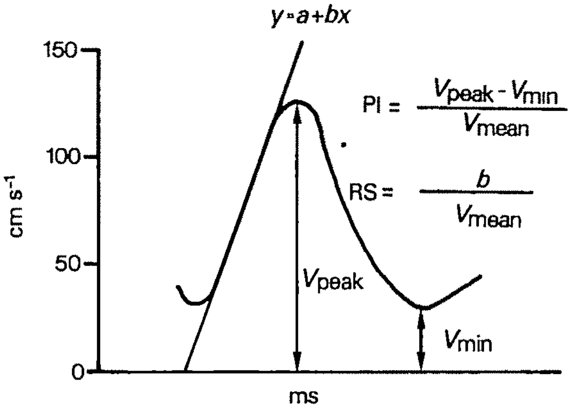
$y = a + bx$
150
100
50
0
cm s^{-1}
$PI = \frac{V_{peak} - V_{min}}{V_{mean}}$
$RS = \frac{b}{V_{mean}}$
V_{peak}
V_{min}
ms

FIG. 1. Diagram of waveform analysis of the fetal aortic maximum velocity. V_{peak} = peak systolic blood velocity; V_{min} = minimum diastolic blood velocity; V_{mean} = mean velocity over the cycle.

Student's paired t test (two-tailed) was used for comparisons within groups, $P < 0.05$ being considered significant.

RESULTS

Preoperative effects on the patients

Figure 2 shows maternal heart rates and arterial pressures before, and 15 and 30 min after, the induction of extradural anaesthesia in the three groups. In group Ea, 15 min after the main dose,

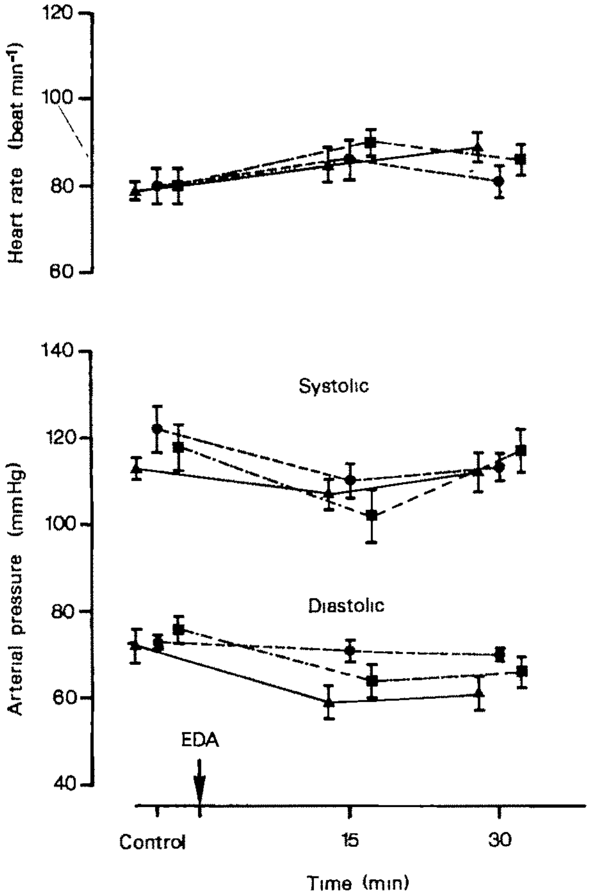

FIG. 2. Maternal arterial pressure and heart rate before, and 15 and 30 min after, induction of extradural anaesthesia (EDA) with 1.5% etidocaine containing adrenaline (▲), 0.5% bupivacaine (●) and 0.5% bupivacaine containing adrenaline (■). Means ± SEM.

there were significant reductions in systolic ($P < 0.05$) and diastolic ($P < 0.01$) arterial pressures, and an increase ($P < 0.05$) in maternal heart rate. The decrease ($P < 0.01$) in diastolic arterial pressure and the increase ($P < 0.01$) in maternal heart rate persisted for 30 min after the main dose. In group Bp, the systolic arterial pressure was decreased significantly ($P < 0.05$) 15 min after the main dose. In group Ba, the diastolic arterial pressure was decreased, both at 15 ($P < 0.01$) and at 30 ($P < 0.05$) min after the main dose. The maternal heart rate was increased ($P < 0.01$) 15 min after the main dose. No instance of cardiac arrhythmia occurred in any of the groups.

Seventeen women were given ephedrine 5–20 mg during the first 30 min after the main dose of the local anaesthetic solution: seven in group Ea, six in group Bp and four in group Ba. The median amount of ephedrine given during this first 30 min was 7.5 mg (range 5–20) in group Ea, 10 mg (range 10–20) in group Bp, and 7.5 mg (range 5–10) in group Ba. The total amounts of ephedrine given during extradural anaesthesia were 100 mg, 125 mg and 95 mg in groups Ea, Bp and Ba, respectively. A systolic arterial pressure less than 90 mm Hg during the first 30 min after the main dose of local anaesthetic was recorded in two women in group Ea, in four women in group Bp, and in two women in group Ba. The hypotensive events were all of less than 2 min duration.

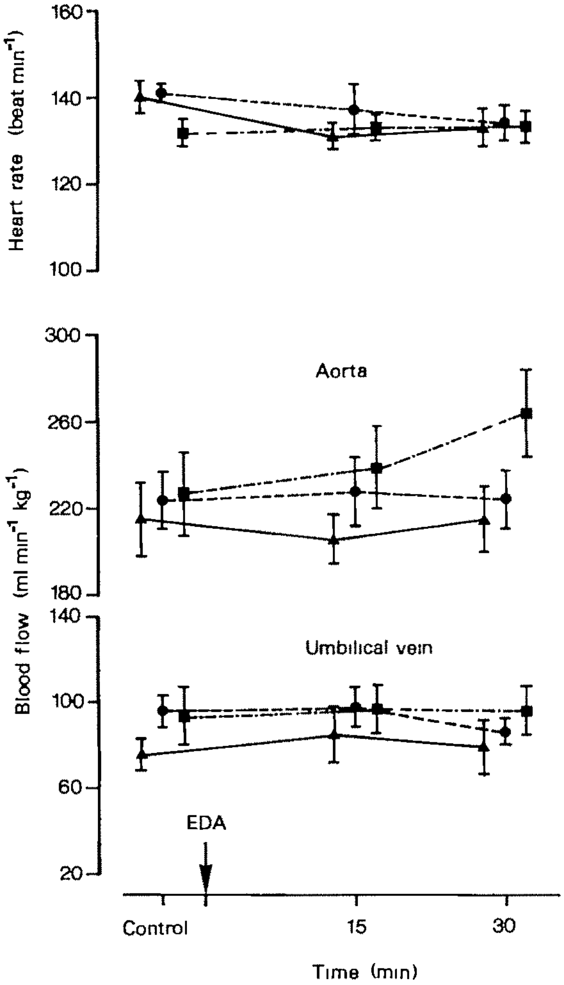

FIG. 3. Fetal heart rate and blood flow measured in the thoracic descending aorta and umbilical vein before, and 15 and 30 min after, induction of extradural anaesthesia (EDA) with 1.5% etidocaine containing adrenaline (▲), 0.5% bupivacaine (●) and 0.5% bupivacaine containing adrenaline (■). Means ± SEM.

TABLE V. *Efficacy of the motor and sensory block. Bromage scale: 1 = unable to move feet and knees; 2 = able to move feet only; 3 = just able to move knees; 4 = full flexion of knees and feet. Sensory block efficacy test: 1 = excellent analgesia; 2 = mild discomfort requiring supplementary analgesia after delivery; 3 = discomfort requiring supplementary analgesia before delivery; 4 = inadequate sensory block–general anaesthesia required. Ea = 1.5% Etidocaine with adrenaline; Bp = 0.5% bupivacaine; Ba = 0.5% bupivacaine with adrenaline*

	Group Ea ($n = 9$)	Group Bp ($n = 9$)	Group Ba ($n = 9$)
Motor block Bromage scale			
1	9	1	0
2	0	6	6
3	0	2	2
4	0	0	1
Sensory block efficacy test			
1	6	5	5
2	3	4	3
3	0	0	0
4	0	0	1

The cephalic spread of cutaneous analgesia is shown in table IV. No difference was found between the three groups. The degree of motor blockade was greatest in group Ea (table V).

Effects on the fetus

Fetal circulatory variables before and after the induction of anaesthesia are shown in figure 3 and table VI. Fetal heart rate decreased ($P < 0.05$) 15 min after the main dose in group Ea, but remained unchanged in the other two groups. Fetal blood flow in the thoracic part of the descending aorta remained unaffected in groups Ea and Bp, but increased ($P < 0.05$) 30 min after the main dose in group Ba. Blood flow in the intra-abdominal part of the umbilical vein remained unaffected in all groups, as did V_{peak}, PI and RS.

Peroperative effects on the women

No circulatory complications occurred during surgery. There was no instance of cardiac arrhyth-

TABLE VI. *Fetal blood flow variables before and after induction of extradural analgesia. Ea = 1.5% etidocaine with adrenaline; Bp = 0.5% bupivacaine; Ba = 0.5% bupivacaine with adrenaline. * Significance of difference between measurements before and 15 min after extradural anaesthesia; ** significance of difference between measurements before and 30 min after extradural anaesthesia; ns = non-significant*

	Group Ea ($n = 9$)			Group Bp ($n = 9$)			Group Ba ($n = 9$)		
	Blood velocity (cm s^{-1})	Vessel diameter (mm)	Pulsatility index	Blood velocity (cm s^{-1})	Vessel diameter (mm)	Pulsatility index	Blood velocity (cm s^{-1})	Vessel diameter (mm)	Pulsatility index
Descending aorta									
Before									
Mean	30.4	7.6	1.97	28.2	7.5	2.21	30.3	7.2	2.11
SD	4.9	0.7	0.37	3.5	0.7	0.29	2.7	0.4	0.28
15 min after									
Mean	27.2	7.7	2.03	27.6	7.6	2.00	29.8	7.3	2.08
SD	4.6	0.7	0.38	4.8	0.8	0.19	4.2	0.4	0.36
P*	ns	ns	ns	ns	ns	ns	ns	ns	ns
30 min after									
Mean	27.3	7.8	1.98	27.4	7.7	1.99	31.8	7.4	2.12
SD	4.0	0.7	0.35	5.7	0.8	0.31	5.2	0.4	0.27
P**	0.038	ns	ns	ns	ns	ns	ns	0.037	ns
Umbilical vein									
Before									
Mean	11.6	7.5		13.8	7.2		10.7	7.6	
SD	2.5	1.2		4.2	0.6		2.2	1.0	
15 min after									
Mean	11.8	7.6		13.0	7.2		12.1	7.4	
SD	2.4	1.2		3.2	1.0		3.5	1.8	
P*	ns	ns		ns	ns		ns	ns	
30 min after									
Mean	11.3	7.3		11.7	6.9		11.9	7.4	
SD	2.2	1.2		2.3	0.5		3.2	0.8	
P**	ns	0.045		ns	ns		ns	ns	

mia. The adequacy of sensory blockade for surgery is given in table V. Pethidine 25–35 mg was given i.v. to three women in group Ea, to four in group Bp, and to three in group Ba. In one patient (group Ba), sensory blockade was unilateral and general anaesthesia was required.

Effects on the newborn

Apgar scores, and umbilical venous and arterial pH, are summarized in table VII. No differences were found between the groups. One newborn in group Ea had an Apgar score of 7 at 5 min and developed respiratory distress syndrome, but recovered within 3 days.

Postoperative effects

There were no late maternal complications caused by the anaesthetic procedure. All but two of the patients stated a preference for extradural anaesthesia at any future Caesarean section. One woman in group Bp, who had experienced the surgical procedure as "violent", stated a preference for general anaesthesia in future. The patient with the unilateral block (group Ba) was undecided as to any future extradural anaesthesia.

DISCUSSION

The combination of real-time linear array ultrasound and the pulsed Doppler technique has opened up new possibilities for non-invasive measurement of human fetal blood flow *in utero* (Eik-Nes, Brubakk and Ulstein, 1980). The accuracy and reproducibility of the blood flow estimations with this technique have been evaluated in methodological studies both *in vitro* and *in vivo*. In an experimental study, the ultrasound/Doppler technique was compared with an electromagnetic method (Eik-Nes et al., 1987). Correlation coefficients between the two methods ranging from 0.89 to 0.98 indicate that the ultrasonic method is reasonably accurate. Except for measurements of vessel diameter, the reproducibility of the ultrasound/Doppler technique is good, both for any given operator and from one operator to another (Lingman, 1985). Even though Eik-Nes and colleagues (1982) showed that the measurement of the diameter of the vessel was the most critical feature of blood flow examinations, maximum errors in volume blood flow did not exceed 10–13% in vessels of diameter 6–8 mm. In the present study, the gestational ages ranged from 37 weeks to 41 weeks, when vessel diameters normally exceed 6 mm.

This ultrasonic technique has been applied in studies of pharmacological effects on fetal circulation of drugs used in pregnancy and labour (Kirkinen and Jouppila, 1983; Lingman, Lundstrom and Marsál, 1986; Montan et al., 1987). As extradural anaesthesia is used commonly during labour and for elective Caesarean section, we considered it important to examine the possible effects on fetal blood flow of extradural anaesthesia induced with the three anaesthetic solutions most commonly used in our Department.

Etidocaine and bupivacaine are both highly protein-bound. The fetal:maternal ratios of etidocaine and bupivacaine concentrations in blood are less than 1.0 (i.e., less of the drug reaches the fetus than is present in the maternal circulation). It has been claimed that this is because of extensive fetal tissue uptake rather than slow placental transfer. In the rabbit, however, fetal tissue uptake could not account for persisting low fetal:maternal ratios of bupivacaine (Carson and Reynolds, 1986). However, no central nervous system effects of etidocaine (Lund et al., 1977) or bupivacaine (Scanlon et al., 1976; McGuinness et al., 1978) have been detected by neurobehavioural testing. Maternal and fetal blood concentrations of etido-

TABLE VII. *Umbilical blood pH and Apgar score. Ea = 1.5% etidocaine with adrenaline; Bp = 0.5% bupivacaine; Ba = 0.5% bupivacaine with adrenaline*

		Group Ea ($n = 9$)	Group Bp ($n = 9$)	Group Ba ($n = 9$)
Umbilical	Mean	7.22	7.22	7.21
arterial pH	SD	0.04	0.05	0.05
Umbilical	Mean	7.32	7.28	7.28
venous pH	SD	0.04	0.04	0.03
Apgar score	at 1 min	1	0	0
< 7	at 5 min	0	0	0

caine (Lund et al., 1977) or bupivacaine (Belfrage et al., 1975) increase rapidly after induction of extradural anaesthesia, and maximum concentrations of bupivacaine have been reported to occur 10–30 min after induction of extradural anaesthesia (Belfrage et al., 1975). This corresponds to the period when the blood flow measurements were performed in the present study.

We were able to confirm that etidocaine induces a profound degree of motor blockade. Adequate sensory blockade was obtained to an equal extent in all three groups, as measured by the frequency of subjective discomfort during the surgery, requirements for supplementary analgesia, and patients' comments.

The inclusion of adrenaline in the local anaesthetic solutions used for extradural anaesthesia has been reported to increase the intensity of the analgesia, but also the frequency of hypotension (Bromage, 1978). In contrast, Levinson and colleagues (1975) found no difference in the frequency of hypotension during extradural anaesthesia, whether or not adrenaline was included in the local anaesthetic. In our study, despite the use of a left lateral tilt to avoid aortocaval compression, preloading infusion and ephedrine, maternal arterial pressure was affected to some extent by extradural anaesthesia with all the three local anaesthetic solutions. The frequency of systolic arterial pressure less than 90 mm Hg was slightly greater in group Bp. The total requirements for ephedrine did not differ between the groups.

In the present study, fetal heart rate was affected only by Ea, and although the decrease in fetal heart rate was significant, it remained within normal limits. The success rate in recording the fetal aortic blood flow was 100 %, and in recording the umbilical venous blood flow 83 %, which is in agreement with the results of other investigators (Eik-Nes et al., 1982). Fetal blood flow in the thoracic part of the descending aorta and in the umbilical vein was not affected by extradural anaesthesia with any of the three local anaesthetic solutions, except for a 12 % increase in fetal aortic blood flow 30 min after induction of extradural anaesthesia with Ba. However, this increase remained within the normal range for aortic blood flow. In a previous study of fetal blood flow during obstetric analgesia (Lindblad, Bernow and Marsál, 1987), we reported an increase in fetal aortic blood flow during labour in parturients given no analgesia, as well as after extradural anaesthesia with bupivacaine. While an increase in fetal aortic blood flow seems to be harmless, a reduction of fetal aortic blood flow has been reported in fetuses in imminent danger of asphyxia (Lingman, Laurin and Marsál, 1986); the aortic velocity tracings of such fetuses also show elimination of the diastolic flow and increased PI. No such changes were observed in the present study.

An increase in fetal heart rate has been reported after the administration of ephedrine to the mother (Wright et al., 1981). Ephedrine was used to treat imminent hypotension in this study. We found no increase in fetal heart rate in the 17 fetuses whose mothers had received ephedrine, probably because of the small doses used.

Ralston, Shnider and deLorimer (1974) found no detrimental effect of ephedrine on uterine blood flow in normotensive pregnant ewes and Hollmén and colleagues (1984) reported no effect of ephedrine on human placental blood flow. When we compared fetal aortic and umbilical blood flows in the 10 fetuses whose mothers had not received ephedrine with the 17 fetuses whose mothers had received ephedrine, we found no difference. Thus, we do not believe the use of ephedrine to have any harmful effect on the fetal blood flow.

In summary, 1.5 % etidocaine with adrenaline 5 μg ml^{-1}, 0.5 % bupivacaine plain and 0.5 % bupivacaine with adrenaline 5 μg ml^{-1} all gave a satisfactory sensory block when used for extradural analgesia. After etidocaine with adrenaline, the motor blockade was more profound, although its greater efficacy in this respect is without advantage to the operator or to the patient. The fetal circulatory variables remained stable and within the normal limits, indicating that extradural anaesthesia with any of the three drug regimens studied is safe for the fetus if maternal hypotension is avoided.

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EFFECTS OF THIOPENTONE OR CHLORMETHIAZOLE ON HUMAN PLACENTAL STEM VILLOUS ARTERIES

J. ALLEN, S. MAIGAARD, J. H. CHRISTENSEN, F. ANDREASEN AND A. FORMAN

SUMMARY

Small placental stem villous arteries were micro dissected from specimens obtained at normal term vaginal delivery (n = 25). *Ring preparations of the vessels were mounted in organ baths and isometric tension was measured. Prostaglandin* $F_{2\alpha}$ *(*$PGF_{2\alpha}$*)* 10^{-7}–10^{-4} *mol litre*$^{-1}$ *produced concentration-dependent contractile responses that were inhibited by thiopentone* 10^{-4}–10^{-3} *mol litre*$^{-1}$ *and by chlormethiazole* 3×10^{-4}–3×10^{-3} *mol litre*$^{-1}$*. Thiopentone* 10^{-4}–10^{-3} *mol litre*$^{-1}$ *and chlormethiazole* 3×10^{-4}–3×10^{-3} *mol litre*$^{-1}$ *decreased the tension in vessels previously treated with* $PGF_{2\alpha}$ 10^{-5} *mol litre*$^{-1}$*. Chlormethiazole* 3×10^{-3} *mol litre*$^{-1}$ *inhibited, and thiopentone* 10^{-4}–10^{-3} *mol litre*$^{-1}$ *abolished contractile responses to 5-hydroxytryptamine. Contractions induced by angiotensin II were inhibited by thiopentone* 10^{-3} *mol litre*$^{-1}$ *and chlormethiazole* 3×10^{-3} *mol litre*$^{-1}$*. The concentrations of the two drugs needed to affect contractile activation of isolated human stem villous arteries exceeded the free plasma concentrations reached during anaesthesia induced by the agents during Caesarean section, and the present results do not suggest any major effects of thiopentone or chlormethiazole on fetal placental vascular resistance during the clinical use of these drugs.*

The induction of anaesthesia with thiopentone in young patients is associated with minimal cardiovascular side effects (Becker and Tonnesen, 1978). In animal models, on the other hand, thiopentone has been found to increase arterial pressure, in line with some findings in man of increased peripheral resistance (Flickinger et al., 1961), despite evidence of decreases in preganglionic sympathetic activity (Millar et al., 1970). When thiopentone is used to provide anaesthesia for Caesarean section, such effects on fetal and maternal placental vessels would constitute important characteristics of the drug, especially when maternal and fetal placental perfusion is impaired—as in pregnancy-induced hypertension. There is no evidence that chlormethiazole, which has been advocated for the treatment of convulsions and the induction of anaesthesia in such patients, has such direct vascular effects (Duffus, Tunstall and MacGillivray, 1968).

The regulation of fetal vascular resistance, by changes in the tension of the smooth muscle in the media, in the human placenta is probably effected through the stem villous arteries, since the more peripherally situated villous vessels seem devoid of medial smooth muscle cells (Kaufmann, 1982). Moreover, the fetal placental vascular bed seems to lack sympathetic innervation (Reilly and Russel, 1977); the maintenance of vascular tone in these vessels may be controlled by prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) and angiotensin II (Rankin and McLaughlin, 1979). A functional role for 5-hydroxytryptamine (5-HT) cannot be excluded, although the contractile effects of this amine seem to decrease with decreasing diameter of the placental arterial tree (Tulenko, 1979).

In order to clarify whether thiopentone or chlormethiazole directly affect human fetal placental vessels, we have compared the effects of these drugs on the contractile responses induced by $PGF_{2\alpha}$, angiotensin II and 5-HT in small, isolated human placental stem villous arteries.

JIM ALLEN, SVEND MAIGAARD, AXEL FORMAN (Department of Obstetrics and Gynecology); JØRGEN H. CHRISTENSEN (Department of Anaesthesiology); Aarhus Kommunehospital, DK-8000 Aarhus, Denmark. FREDERIK ANDREASEN, Institute of Pharmacology, Division of Clinical Pharmacology, University of Aarhus, Aarhus, Denmark. Accepted for Publication: November 7, 1986.

Correspondence to J.A.

MATERIAL AND METHODS

Samples of placental tissue were obtained from macroscopically normal areas of the chorionic plate at normal, term vaginal deliveries ($n = 25$). Only specimens obtained within 20 min of delivery were used. The samples were transported immediately to the laboratory in ice-cold Krebs solution (for composition, see below). Small stem villous arteries (outer diameter 500–600 μm) were identified microscopically *in situ* after the injection of a fine suspension of methylene blue in Krebs solution (1:50) to the chorionic arteries, and dissected free by use of microscissors. Tubal segments (1.0–1.2 mm) of the vessels were prepared and transferred to water-mantled, 5-ml organ baths containing Krebs solution (37.0 ± 0.5 °C) aerated with carbogen (5% carbon dioxide in oxygen). The final pH was 7.40 ± 0.05. The vessels were mounted on the short, parallel legs of two L-shaped stainless steel hooks as described previously (Högestätt, Andersson and Edvinsson, 1983). One of the hooks was attached to a Grass Ft 03 transducer and the other connected to a displacement device which allowed adjustments of passive tension. Thus, "isometric" tension was measured. The preparations were allowed to equilibrate for 1–2 h, during which time passive tension was adjusted to 3 mN/mm vessel length. Previous studies have shown that, at this basic tension, near-optimum mechanical responses to potassium 124 mol litre^{-1} depolarization (see below) are obtained (Maigaard, Forman and Andersson, 1986a). Some of the dissected preparations were stored overnight at 4 °C in Krebs solution. This procedure did not influence the mechanical responses to the drugs.

Contractions were induced by exposure to high-potassium Krebs solution at 20-min intervals until they were reproducible—less than 10% difference between two subsequent contractions. Responses to drugs during the investigation were expressed as per cent of the mean of these initial potassium-induced responses, which could be reproduced in control preparations throughout the investigation. If reproducible responses to potassium depolarization could not be obtained, the preparation was discarded.

Contractions were induced by the cumulative addition of $PGF_{2\alpha}$ and 5-HT alone, and in the presence of thiopentone or chlormethiazole. Tachyphylaxis to angiotensin II develops rapidly in human stem villous arteries (Maigaard, Forman and Andersson, 1986a), and effects on single responses to angiotensin II 10^{-5} mol litre^{-1} were used to evaluate the effects of pretreatment with the two drugs on contractile activation induced by the peptide. Furthermore, thiopentone and chlormethiazole were added cumulatively to preparations precontracted by $PGF_{2\alpha}$ 10^{-5} mol litre^{-1}, and relaxation was expressed as a per cent of the initial tension.

Solutions

Normal Krebs (mmol litre^{-1}): NaCl 119, KCl 4.6, $NaHCO_3$ 15, $CaCl_2$ 1.5, $MgCl_2$ 1.2, NaH_2PO_4 1.2, glucose 11.

High potassium Krebs (mmol litre^{-1}): KCl 124, $NaHCO_3$ 15, $CaCl_2$ 1.5, $MgCl_2$ 1.2, NaH_2PO_4 1.2, glucose 11.

Drugs

Prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, Dinoprost, Upjohn); 5-HT (serotonin, Sigma); angiotensin II (Hypertensin, Ciba); chlormethiazole (Heminevrin, Astra); thiopentone (Thiopental, Løvens kemiske Fabrik).

RESULTS

Results are expressed as mean ± SEM.

None of the stem villous arterial preparations exhibited spontaneous contractile activity. The addition of thiopentone 10^{-7}–10^{-3} mol litre^{-1} or chlormethiazole 10^{-7}–10^{-3} mol litre^{-1} did not produce any changes in resting tension, which remained constant throughout each study.

Effects of thiopentone or chlormethiazole on $PGF_{2\alpha}$-induced contractile responses

$PGF_{2\alpha}$ 10^{-7}–10^{-4} mol litre^{-1} induced a concentration-related increase in tension, which reached a maximum of 91.3 ± 6.7% (± SEM, $n = 7$) of the initial potassium control contraction at a $PGF_{2\alpha}$ concentration of 3×10^{-5} mol litre^{-1} (fig. 1).

Pretreatment with thiopentone in concentrations up to 10^{-5} mol litre^{-1} had no significant potentiating or inhibitory effects, while thiopentone 10^{-4}–10^{-3} mol litre^{-1} inhibited the responses to the cumulative addition of $PGF_{2\alpha}$ 10^{-7}–10^{-4} mol litre^{-1} (fig. 1). The cumulative addition of thiopentone 3×10^{-5}–10^{-3} mol litre^{-1} to vessels precontracted by $PGF_{2\alpha}$ 10^{-5} mol litre^{-1} caused concentration-related relaxation by up to 96.8 ± 4.4% (± SEM, $n = 7$), while thiopentone

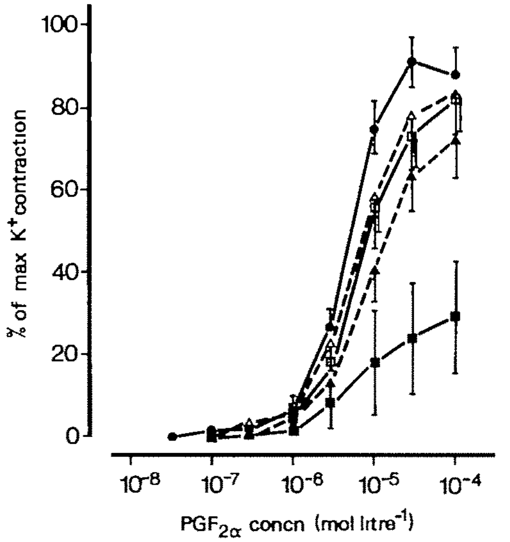

FIG. 1. Isolated human stem villous arteries. Concentration related contractile effects of PGF$_{2\alpha}$ in control preparations (●) and after pretreatment with thiopentone 10^{-4} mol litre^{-1} (□), thiopentone 10^{-3} mol litre^{-1} (■), chlormethiazole 3×10^{-4} mol litre^{-1} (△) and chlormethiazole 3×10^{-3} mol litre^{-1} (▲). Mean ± SEM, $n = 7$.

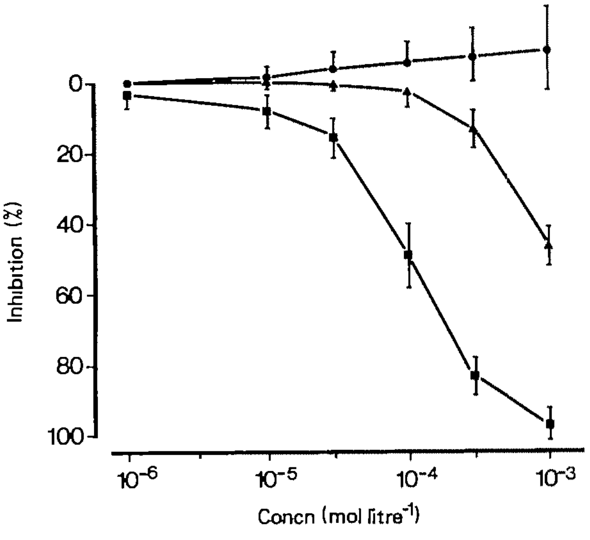

FIG. 2. Isolated human stem villous arteries. Concentration-dependent inhibitory effects of thiopentone (■) and chlormethiazole (▲) on tension induced by PGF$_{2\alpha}$ 10^{-5} mol litre^{-1} compared with controls (●). Mean ± SEM, $n = 7$.

in concentrations of 10^{-5} mol litre^{-1} and below had no significant effect (fig. 2).

Pretreatment with chlormethiazole 3×10^{-4}–3×10^{-3} mol litre^{-1} induced minor inhibition of the contractions produced by PGF$_{2\alpha}$ 10^{-7}–10^{-4} mol litre^{-1} (fig. 1), and pretreatment with lower concentrations of chlormethiazole did not change the mechanical responses to PGF$_{2\alpha}$. When added cumulatively to preparations precontracted by PGF$_{2\alpha}$ 10^{-5} mol litre^{-1}, chlormethiazole 3×10^{-4}–10^{-3} mol litre^{-1} induced relaxation by up to 46.6 ± 5.6% (±SEM, $n = 7$), while lower concentrations of the drug did not cause significant changes in tension induced by PGF$_{2\alpha}$ 10^{-5} mol litre^{-1} when compared with controls (fig. 2).

Effects of thiopentone or chlormethiazole on contractile responses to 5-HT

5-HT 10^{-8}–10^{-5} mol litre^{-1} induced a minor, often inconstant increase in tension reaching a maximum of 9.3 ± 3.0% (±SEM, $n = 7$) of the potassium control response at a 5-HT concentration of 10^{-5} mol litre^{-1}. Tachyphylaxis developed rapidly, and steadily increased tension could not be induced by the amine. Pretreatment with thiopentone 10^{-4}–10^{-3} mol litre^{-1} abolished the responses to 5-HT ($n = 7$). Potentiating effects of lower concentrations of thiopentone on responses to 5-HT were not observed. Pretreatment with chlormethiazole 3×10^{-4} mol litre^{-1} had no significant effects, while chlormethiazole 3×10^{-3} mol litre^{-1} inhibited contractile responses to 5-HT 10^{-5} mol litre^{-1} by about 40% (not significant, $n = 7$).

Effects of thiopentone or chlormethiazole on contractile responses to angiotensin II

Angiotensin II 10^{-6} mol litre^{-1} induced a transient contraction of the stem villous arterial preparation amounting to 20.0 ± 4.7% of the initial potassium control contraction (±SEM, $n = 7$). Pretreatment with thiopentone 10^{-4} mol litre^{-1} or chlormethiazole 3×10^{-4} mol litre^{-1} had no significant effects on this response. Pretreatment with thiopentone 10^{-3} mol litre^{-1} decreased the angiotensin II 10^{-5} mol litre^{-1} response to 5.8 ± 5.8% of the potassium control, while chlormethiazole 3×10^{-3} mol litre^{-1} decreased the response to 12.7 ± 3.5% of the potassium control (±SEM, $n = 7$).

DISCUSSION

Previous studies of the effects of thiopentone on squid giant axons (Sevcik, 1980) and isolated vessels (Andreasen and Christensen, 1984; Fukuda et al., 1984) have indicated that the drug has pre- and postjunctional effects. Thus thiopentone 3×10^{-5}–1.4×10^{-3} mol litre^{-1} increased basic tension in the isolated rabbit pulmonary artery. Moreover, contractions induced by electrical field stimulation were enhanced by thiopentone up to 2.4×10^{-4} mol litre^{-1}, while a further increase in concentration of the drug caused a gradual decrease in the amplitude of these responses. Finally, thiopentone 5.6×10^{-4} mol litre^{-1} potentiated the contractile responses to low concentrations of noradrenaline, but depressed the effects of higher concentrations of the amine. In rabbit aorta, however, noradrenaline-induced contractions were consistently potentiated (Price and Price, 1962).

In the present study, performed on human fetal placental vessels which lack sympathetic innervation (Reilly and Russel, 1977), thiopentone (in concentrations up to 10^{-3} mol litre^{-1}) had no effect on basal tension. Furthermore, the drug consistently produced non-specific inhibition of responses to PGF$_{2\alpha}$, angiotensin II and 5-HT—compounds of suggested importance for the maintenance of fetal placental smooth muscle tension. Effects on noradrenaline-induced contractions were not tested, since human villous arteries show only weak, sometimes inconstant, responses to this amine (Maigaard, Forman and Andersson, 1986b). Whether endogenous mechanisms for vascular relaxation, like synthesis, release or smooth muscle effects of relaxant substances, are affected by thiopentone was not tested in the present study, and cannot be entirely excluded. Nevertheless, the present and previous findings suggest that a non-specific inhibition of contractile activation is an important direct smooth muscle effect of high concentrations of thiopentone.

Chlormethiazole is considered to cause only minor cardiovascular side effects (Wilson, Stephen and Scott, 1969), in line with clinical experience when using the compound for anaesthesia in pregnancy-induced hypertension (Kristoffersen, 1984). The present study demonstrated the non-specific inhibitory effects of high concentrations of the drug, while lower concentrations did not affect contractile activation of the isolated stem villous arteries. The results do not permit any conclusions as to the site of action of the drug, except that prejunctional sympathetic effects seem excluded in these vessels.

Whether the inhibitory effects on contractile activation of isolated stem villous arteries observed with high concentrations of both drugs are of clinical importance depends on the actual tissue concentrations achieved during anaesthesia. Pharmacokinetic studies of thiopentone in fetal cord blood during Caesarean section have revealed concentrations up to 2.1×10^{-5} mol litre^{-1} and maternal plasma concentrations of up to 1.3×10^{-4} mol litre^{-1} (free ± protein bound) (Christensen, Andreasen and Jansen, 1981). When chlormethiazole was used for anaesthesia during Caesarean section, fetal cord blood concentrations of 10^{-4} mol litre^{-1} and maternal plasma concentrations of 1.4×10^{-4} mol litre^{-1} have been reported (Duffus, Tunstall and MacGillivray, 1968). Although recent findings suggest that the protein-bound fraction of thiopentone cannot be considered totally inert (Andreasen and Christensen, 1984), the "active" drug concentration to which the vessels are exposed is still considerably lower than the total plasma concentration. Thus, the present results obtained in protein-free Krebs solution do not suggest that thiopentone or chlormethiazole would induce any major effects on placental vascular resistance during the clinical use of these drugs. However, their effects could, conceivably, be of relevance in any situation in which the concentration of plasma protein is low—as is seen occasionally in pregnancy-induced hypertension. Unspecific inhibition of fetal placental vascular contractile activation might decrease vascular resistance, but whether fetal placental blood flow would remain unaffected would depend on the systemic fetal cardiovascular response to such treatment.

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HIGH PEEP DECREASES HYALINE MEMBRANE FORMATION IN SURFACTANT DEFICIENT LUNGS

E. P. ARGIRAS, C. R. BLAKELEY, M. S. DUNNILL, S. OTREMSKI AND M. K. SYKES

SUMMARY

Lung lavage was performed in 16 anaesthetized rabbits to produce surfactant-deficient lungs. This resulted in alveolar collapse, an arterial P_{O_2} of less than 15 kPa on 100% oxygen and an inflection point on the inspiratory limb of the pressure–volume curve at an airway pressure of 8–10 mm Hg. One group of eight animals was then ventilated with a positive end-expiratory pressure (PEEP) equal to the pressure at the inflection point, whilst the second group of eight was ventilated with a PEEP 5 mm Hg less than the inflection point. Animals in the high PEEP group had a significantly greater arterial P_{O_2} than those in the low PEEP group, but the mean survival time for each group was similar. However, there was a significantly greater incidence of hyaline membranes in the low PEEP group. Various mechanisms to explain these findings are discussed.

In premature neonates with the respiratory distress syndrome (NRDS) there is a reduction in surfactant and an increase in surface tension forces in the terminal airways and alveoli. This leads to an increase in lung elastic recoil and alveolar collapse. The increase in surface tension also increases the pressure gradient for fluid filtration across the pulmonary capillaries and hinders the movement of the air–liquid interfaces through the narrow terminal airways. The high transpulmonary pressures generated in an attempt to maintain normal tidal volumes tend to overdistend preterminal air spaces and also cause epithelial damage, the desquamated cells condensing with the protein rich filtrate to form the characteristic hyaline membranes (Nilsson, Grossman and Robertson, 1980). The high transpulmonary pressures may also result in shear stress forces between contiguous collapsed and expanded alveoli, so causing further lung damage (Menkes et al., 1972).

Two recent studies have suggested that the formation of the hyaline membranes in NRDS might be prevented by the use of apnoeic oxygenation (Pesenti et al., 1982) or high frequency oscillation (Hamilton et al., 1983). The common feature in these studies was the reduction in tidal volume and peak airway pressure, and the prevention of alveolar collapse throughout the ventilatory cycle. If the prevention of collapse, and not the pattern of ventilation itself, is the important factor it should be possible to prevent the formation of hyaline membranes with conventional mechanical ventilation, provided that alveolar units are held open throughout by an appropriate PEEP. In order to study the problem further we induced surfactant deficiency in rabbits by lung lavage with saline (Lachmann et al., 1982) and compared the effects of conventional mechanical ventilation with high and low PEEP on arterial P_{O_2}, lung mechanics and lung histology.

MATERIALS AND METHODS

New Zealand White rabbits ($n = 16$) (2–3.5 kg) were premedicated with fentanyl-plus-fluanisone (Hypnorm, Janssen) 0.3 ml kg^{-1}, and anaesthesia was induced with halothane in oxygen. Tracheotomy was performed and a 4-mm i.d. plastic (Portex) tracheal tube inserted, leaks being prevented by ligatures around the trachea. Main-

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E. P. ARGIRAS, M.D.; C. R. BLAKELEY, M.B., CH.B., M.R.C.P., F.F.A.R.C.S.; S. OTREMSKI, M.D.; M. K. SYKES, M.A., M.B., B.CHIR., F.F.A.R.C.S., HON. F.F.A.R.A.C.S.; Nuffield Department of Anaesthetics, Radcliffe Infirmary, Oxford OX2 6HE. M. S. DUNNILL, M.D., F.R.C.P., F.R.C.PATH., Department of Histopathology, John Radcliffe Hospital, Oxford. Accepted for Publication: April 1, 1987.

Correspondence to M.K.S. (Radcliffe Infirmary).

tenance of anaesthesia was with bolus doses of Hypnorm 0.1 ml i.v. Pancuronium 1 mg was administered every 20 min. Arterial and venous cannulae were placed in opposite ears. Mechanical ventilation was initiated at 30 b.p.m. using a T-piece system, the expiratory limb of which was occluded by an electronically controlled Siemens valve. Fresh gas flow, frequency and inspiratory to expiratory (I:E) time ratio could be varied independently. A positive end-expiratory pressure (PEEP) was provided by a magnetic valve (Instrumentation Industries). An FI_{O_2} of 1 was maintained throughout. The animal was placed on a warming blanket to maintain body temperature at 38±1 °C and ECG leads secured. Arterial and airway pressures were measured continuously using Gould T105 AD transducers connected to an Electromed MX 216 two-channel recorder. Rectal temperature was recorded using an I.D.P. Series 3 monitor. Blood-gas tensions were measured not less than hourly on an ABL 2 automatic analyser (Radiometer, Copenhagen). In six animals a catheter was inserted to the right ventricle via the right jugular vein, for measurement of mixed venous oxygen tension. After stabilization, arterial blood-gas tensions were measured and an initial static pressure–volume loop was performed by injecting 3–5 ml aliquots of air to the lung from a syringe at 3-s intervals, up to a maximum inflating pressure of 25 mm Hg. This value was chosen because the inflection point on the ascending limb could be clearly identified, whilst higher values risked the development of a pneumothorax or sudden cardiac arrest. The volume was derived from a Fleisch pneumotachograph head, Statham PD45 differential transducer and electronic integrator, and the trace was drawn by a Bryans 29000 A3 X–Y recorder (fig. 1).

Surfactant depletion was then produced by lavage of the lung with isotonic saline 20 ml kg^{-1} at 37 °C injected from a syringe directly to the tracheal tube whilst airway pressure was monitored to ensure that this remained less than 25 mm Hg. The saline was aspirated immediately. Between lavages mechanical ventilation was maintained with a peak airway pressure of 20 mm Hg and PEEP of 3 mm Hg. Lavages were continued at 5-min intervals until the arterial P_{O_2} was less than 15 kPa. This usually required four lavages, one fewer than used by Lachmann and colleagues (1982) who used five lavages and decreased the Pa_{O_2} to 6 kPa.

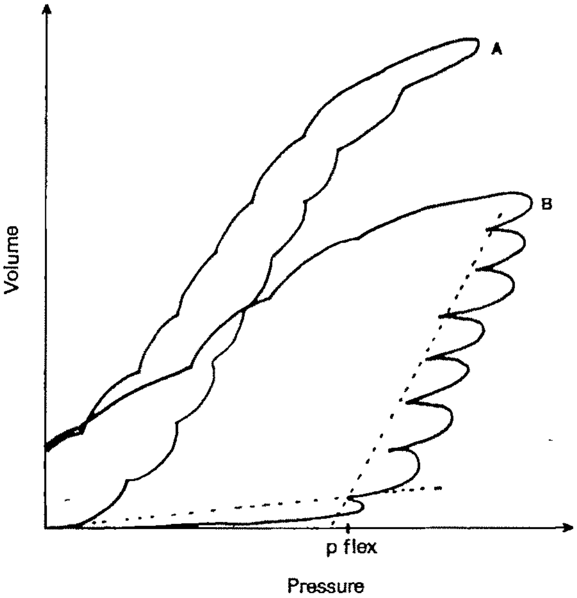

FIG. 1. Pressure–volume curve, before (A) and after (B) lavage. p flex = inflection point.

Five minutes after the last lung lavage the pressure–volume loop was repeated and the inflection point (p flex) determined (fig. 1). A sustained lung inflation to 15 mm Hg for 15 s was then performed to recruit alveoli before establishing the pattern of ventilation and the animals were divided randomly into two groups of eight. One group was ventilated with PEEP equal to the measured inflection point pressure, the other with PEEP set 5 mm Hg less than this pressure. Peak pressure was limited to 25 mm Hg in both groups and the frequency of ventilation was adjusted to provide normocapnia. Ventilation was continued in this manner until the death of the animal. One animal from each group was excluded from the results shown because death occurred within 3 h of lavage, which was the minimum period prescribed in our study in order to ensure that there was adequate time for the hyaline membrane to develop. Pressure–volume loops were repeated shortly before death in four animals, and found to be similar to those performed immediately after lavage.

After death the trachea, major bronchi and lungs were carefully excised. One bronchus was tied off and the lung removed. The other lung was inflated with formol–saline to a pressure of 20 cm H_2O via the trachea, and both lungs were then fixed in formol–saline. However, under light microscopy there was no difference in the degree of hyaline membrane formation in the two lung specimens. Blocks of tissue were taken from both upper and lower zones, processed for paraffin embedding and sections cut at 5 μm were stained with haematoxylin and eosin. At least three sections across the entire lung field were examined before grading for hyaline membrane formation. The lung sections were graded on a scale of 0–4 for the presence of hyaline membranes and intra-alveolar neutrophil infiltrate, by a pathologist (M.S.D.) who was unaware of the group to which the animal belonged. The differences in hyaline membrane score, neutrophil score and arterial Pa_{O_2} were compared by Mann–Whitney *U* test, and an unpaired *t* test was applied to the differences in mean airway pressures.

RESULTS

The two groups of rabbits were comparable in terms of weight, initial arterial pressure, airway pressure, and blood-gas tensions. The initial pressure–volume loops were measured to determine the pre-lavage inspiratory compliance (mean 3.35 ml/cm H_2O, range 2.5–4.5) from the slope of the inspiratory curve. Table I shows the blood-gas tensions and airway pressures in the two groups: (a) before lavage; (b) immediately after lavage; (c) after stabilization on the selected mode of ventilation for 1 h; (d) during the last 1 h of the study.

After lavage the inflection point on the ascending limb of the pressure–volume loop was between 8 and 10 mm Hg in all the animals. The loops performed at the end of six of the studies (three from each group) did not show any significant change from those obtained after lavage. The arterial Po_2 after stabilization at the selected PEEP (stage c) was significantly greater in the high PEEP group ($P < 0.0001$). In some of the latter animals it was possible to restore the Pa_{O_2} almost to the pre-lavage value. The pH and Pa_{CO_2} in the two groups were similar at all stages in the studies, although it should be noted that sodium bicarbonate was given as appropriate for correction of metabolic acidosis. Although the peak airway pressure in the two groups was the same, the high PEEP group had a significantly higher mean airway pressure (MAP) than the low PEEP group ($P < 0.005$). In an effort to determine whether this affected the cardiac output we inserted a right ventricular catheter in six animals, three from each group, to measure the arterio–venous oxygen content differences (table II). Although there were wide variations, the oxygen content differences, measured 2 h after lavage, tended to be greater in the high PEEP group, suggesting that the cardiac output in this group may have been lower. There was no significant difference in crude survival time (high PEEP group 6 h 50 min, low PEEP group 6 h 28 min), but death in the low PEEP group was invariably associated with severe hypoxaemia, whereas in the high PEEP group the arterial oxygen tension immediately before death was still similar to baseline (mean Pa_{O_2} 46.3 kPa). These animals suffered a rapid and inexorable decline in arterial pressure shortly before death. It seems likely,

TABLE I. *Mean (SD) blood-gas tensions and pH, and peak and mean airway pressures in the high and low PEEP groups, (a) before lavage; (b) immediately after lavage; (c) 1 h after lavage; (d) during the last 1 h of the study. Differences in* Pa_{O_2} *for stages (c) and (d) are significant* ($P < 0.001$)*; differences in mean airway pressure for (c) and (d) are significant* ($P < 0.005$)

	(a)	(b)	(c)	(d)
Pa_{O_2} (kPa)				
High PEEP	65.4 (6.7)	7.77 (1.6)	57.6 (9.4)	49.7 (1.7)
Low PEEP	62.9 (8.5)	9.87 (1.9)	9.84 (3.5)	6.53 (0.6)
Pa_{CO_2} (kPa)				
High PEEP	4.33 (1.1)	5.49 (1.4)	5.88 (1.1)	5.72 (1.2)
Low PEEP	3.85 (0.8)	5.34 (0.6)	4.16 (0.9)	4.82 (0.8)
pH				
High PEEP	7.41 (0.1)	7.30 (0.1)	7.30 (0.08)	7.33 (0.07)
Low PEEP	7.44 (0.07)	7.33 (0.05)	7.36 (0.1)	7.31 (0.06)
Peak/mean airway pressure (mm Hg)				
High PEEP	11.7/3.51	15.7/6.7	21.1/12	22.5/12.7
Low PEEP	11.2/3.38	16.7/6.1	21.4/9.1	24.1/10.0

TABLE II. *Arterio–venous differences in oxygen content (vol%) in three animals from each group*

	Before lavage			After lavage			2 h after lavage		
Group	Art.	Ven.	Diff.	Art.	Ven.	Diff.	Art.	Ven.	Diff.
Low	15.4	5.0	10.4	10.9	4.0	6.9	12.4	5.6	6.8
Low	14.2	7.4	6.8	7.2	2.0	5.2	9.9	3.9	6.0
Low	—	—	—	11.9	5.8	6.1	13.7	5.15	8.55
Mean difference			8.6			6.0			7.1
High	18.5	11.2	7.3	17.2	8.5	8.7	16.0	4.5	11.5
High	15.1	6.6	8.5	12.7	4.9	7.8	12.1	3.0	9.1
High	17.9	12.4	5.5	15.5	8.4	7.1	15.3	6.4	8.9
Mean difference			7.1			7.8			9.8

TABLE III. *Histological results for each animal in chronological order, whether high or low PEEP used, with score on a scale of 0–4 for hyaline membrane formation (HM) and neutrophil infiltration (NI). Average scores were HM = 2.7 and NI = 2.7 for low PEEP; HM = 0.7 and NI = 2.1 for high PEEP (difference for HM significant (P < 0.001), for NI not significant)*

	Right lung		Left lung	
Series No.	HM	NI	HM	NI
1. low	4	2	3	2
2. high	1	1	1	1
3. high	2	2	1	3
4. high	0	4	2	4
5. low	4	4	3	3
6. high	2	4	0	3
7. low	3	2	2	2
8. low	2	3	3	3
9. low	4	4	4	3
10. high	0	0	0	3
11. low	4	3	3	3
12. high	0	1	0	2
13. low	3	3	1	2
14. high	0	0	1	2

therefore, that cardiac output was low in both groups.

In those lungs in which membrane formation was pronounced some infiltration of the membrane material by neutrophils could be seen. The appearances closely resembled those seen in the human neonate with the respiratory distress syndrome, with thick homogeneous eosinophilic material stretched across the mouths of the alveolar ducts and respiratory bronchioles. Table III shows both the individual results for each animal, in the order that the studies were performed, and the mean scores for the two groups. The high PEEP animals had significantly lower scores for hyaline membrane formation ($P > 0.001$). The different appearances of the high and low PEEP groups are illustrated in figure 2.

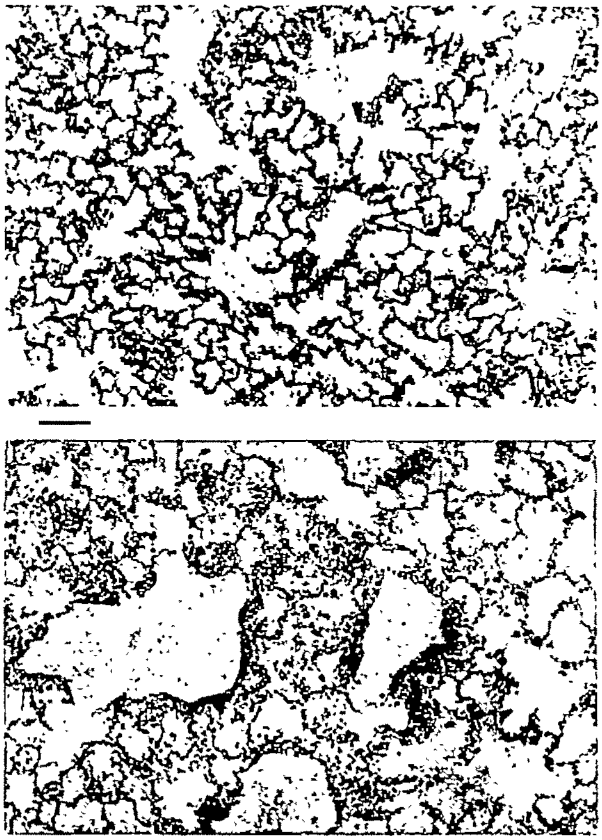

FIG. 2. Rabbit lung. Top: high PEEP group; minimal hyaline membrane formation. Below: low PEEP group; marked hyaline membrane formation. Horizontal bar represents 80 μm.

DISCUSSION

The neonatal respiratory distress syndrome is associated with a deficiency of pulmonary surfactant, a phospholipid mixture which facilitates lung aeration after birth and stabilizes the terminal air spaces. The presence of hyaline membranes is a characteristic feature of this disorder. Necrotic epithelium, fibrin and other plasma proteins, and products of red cell breakdown are present in the membranes, which are formed by the condensation of these substances passing from the blood into the interstitial spaces and through the damaged epithelial lining, which breaks down when surfactant is deficient (Taghizadeh and Reynolds, 1976). The principal sites of hyaline membrane formation are the respiratory bronchioles and alveolar ducts.

The experimental model of NRDS used in this study was originally described by Lachmann (Lachmann, Robertson and Vogel, 1980) in guinea pigs, and, subsequently, in rabbits (Lachmann et al., 1982). It has been used by several other workers in this field (Kolton et al., 1982; Hamilton et al., 1983; Quan et al., 1984). Others (Pesenti et al., 1982; Truog et al., 1984) have preferred to use premature animals. The lavage model has the advantage of simplicity, stability and reproducibility and the histological features are very similar to those seen in the neonatal respiratory distress syndrome, although surfactant production is probably not impaired.

As we found that high inflating pressures tended to cause severe cardiac depression and, occasionally, a pneumothorax, we limited the pressure during the washouts, and the static pressure–volume loops to 25 mm Hg. This is lower than Lachmann's 40 cm H_2O maximum but, in pilot studies, the same histological features were found.

The concept of using the inflection point on the ascending limb of a static pressure–volume curve to indicate the closing volume—or alternatively the reopening of alveoli or small airways—has been well established by comparison with the nitrogen washout technique (Ingram, O'Cain and Fridy, 1974; Demedts et al., 1975) and in cadaver studies (Salmon et al., 1981). It has also been used in studies of NRDS by other workers (Kolton et al., 1982; Pesenti et al., 1985). A similar inflection point has been seen in the early stages of the adult respiratory distress syndrome and Lemaire and co-workers (1981) suggested that it could be used to determine the minimum PEEP which would produce a marked reduction in pulmonary shunt. This suggestion is supported by the study of Pesenti and associates (1985) in lambs with respiratory insufficiency following lung lavage with saline. However, Holtzapfel and colleagues (1983) have suggested that the inflection point on the expiratory limb of the curve is the best indicator of the level of PEEP required to improve oxygenation.

The pressure–volume loops in our study clearly demonstrated reductions in total lung compliance at low lung volumes (mean 0.6 ml/cm H_2O, range 0.48–1.1) after lung lavage. The inflection point occurred consistently between airway pressures of 8 and 10 mm Hg, the slope of the inflation limb of the curve above this point being similar to that observed in the normal lung (mean 2.8 ml/cm H_2O, range 1.5–3.7). By setting the PEEP at the inflection point in one group of animals, and 5 mm Hg below it in the other group we hoped to prevent alveolar and small airways collapse throughout the entire ventilatory cycle in the high PEEP group, whereas in the low PEEP group collapse and re-expansion would have been expected to occur during each ventilatory cycle.

As would have been expected from the differences in end-expiratory lung volume there were striking differences in oxygenation between the high and low PEEP groups. This confirms the findings of Kolton and colleagues (1982) and Hamilton and co-workers (1983) whilst using high frequency oscillation and by Lachmann and co-workers (1982) using prolonged inspiratory times or high values of PEEP.

There were also significant differences in hyaline membrane scores between the high and low PEEP groups. This implies that the maintenance of lung volume is also important in the prevention of the progression from surfactant deficiency to hyaline membrane formation. An interesting comparison can be made between our work and that of Hamilton and co-workers (1983) in this respect. These authors described two groups, one ventilated with conventional mechanical ventilation and one with high frequency oscillation, with significantly less hyaline membrane formation in the latter group. The conventional mechanical ventilation group in Hamilton's paper was ventilated with a mean airway pressure of 15 cm H_2O and PEEP of 6 cm H_2O, and although the mean airway pressure was higher in their experiments than in ours, it seems likely that the lungs were being allowed to collapse at end-inspiration. This would explain our very similar findings. In Hamilton's second group, with HFO at a mean airway pressure of 15 cm H_2O, it seems unlikely that lung volume would have decreased to the value at which alveolar collapse occurs, because this group had higher lung volumes despite being matched for mean airway pressure. This was possibly the result of gas trapping. The histological findings in this group and our own high PEEP group were again comparable. It thus seems probable that it is not the mode of ventilation that is of critical importance, but the maintenance of lung volume. The observation of Pesenti and associates (1982) that hyaline membrane formation can be prevented by the use of apnoeic oxygenation with a constant inflation pressure of 15 cm H_2O further supports this concept.

It should be noted that Truog and colleagues (1983, 1984) failed to demonstrate any difference between conventional mechanical ventilation and high frequency oscillation in two groups of premature monkeys. They suggested that this might be because of differences in lung structure between the two groups, or the nature of the injury at the cellular level. However, the primate model is one of established hyaline membrane disease, whereas workers with the surfactant depletion model have attempted to prevent hyaline membrane formation. It may be that, once hyaline membrane formation is established, high frequency oscillation or other methods of maintenance of lung volume are of diminished value.

Hamilton and colleagues (1983) matched their two groups for mean airway pressure, whereas our high PEEP group had a greater mean airway pressure (12 mm Hg *v.* 9.1 mm Hg). Although we were not able to quantify the effect that this may have had on pulmonary blood flow, it is possible that there may have been an alteration in the relationship between the hydrostatic and oncotic pressures in the pulmonary vessels, with a reduction in the formation of hyaline membrane. Webb and Tierney (1974) demonstrated that ventilation-induced pulmonary oedema in rats produced by high peak airway pressures was prevented by a PEEP of 10 cm H_2O. However, Hopewell and Murray (1976) and Caldini, Leith and Brennan, (1975) demonstrated that high values of PEEP did not reduce the formation of pulmonary oedema in dogs. In order to dissociate the influences of PEEP and mean airway pressure on hyaline membrane formation it would be necessary to change these variables independently.

The results of this study suggest that the maintenance of an adequate lung volume is an important factor in the prevention of the formation of hyaline membrane in surfactant-depleted lungs, and supports the previous findings of Hamilton and colleagues (1983) using high frequency oscillation and of Pesenti and colleagues (1982) using apnoeic oxygenation in this respect. The mechanism of this protection remains a matter of speculation.

In surfactant-deficient lungs there are regional variations in lung compliance, which result in an uneven response to a given inflating pressure and which may thus generate intraregional stresses (Mead, Takashima and Leith, 1970; Hughes, Hoppin and Mead, 1972; Menkes et al., 1972). During conventional mechanical ventilation these stresses may cause regional variations in expansion and so destroy the integrity of the bronchiolar epithelium and alveolar capillary membrane, leading to hyaline membrane formation. By maintaining lung volume and preventing cyclical collapse and re-expansion of airways, the progression to hyaline membrane formation does not occur.

Support for this view may be found in the work of Schweiler and Robertson (1976) and Nilsson, Grossmann and Robertson, (1980). Schweiler and Robertson argued that, in atelectatic lungs, the air–liquid interface exists in the terminal conducting airways rather than in the alveoli, and suggested that when the necessary high distending force is applied to this interface the bronchiolar wall expands and the epithelium is disrupted, leading ultimately to hyaline membrane formation. Nilsson and colleagues used a standard high inflating pressure in two groups of premature rabbits, one of which had been pretreated with surfactant. Only the non-treated group showed prominent damage to the bronchiolar epithelium. They concluded that the epithelial lesions are secondary to an abnormal expansion pattern. Hughes, Hoppin and Mead (1972) demonstrated, in excised dog lungs, that changes in bronchial length and diameter at full inflation were in many cases greater than would have been predicted from the behaviour of the airways dissected free from lung tissue, suggesting that bronchi *in situ* are exposed to distending forces in excess of transpulmonary pressure.

In the low PEEP group it is quite possible that lung units remain collapsed throughout the ventilatory cycle. However, atelectasis *per se* does not induce hyaline membrane formation. One must, therefore, invoke a mechanism which prevents the progression to hyaline membrane formation if lung units are inflated, or causes the progression if they are not. Wyszogrodski and co-workers (1975) have demonstrated that the inactivation of surfactant caused by the hyperventilation of previously normal lungs can be prevented by the application of relatively low values of PEEP (2.5 cm H_2O). Faridy (1976) has shown that distension of dog lungs depleted of surfactant by saline lavage enhances the repletion of surfactant, although it was also observed that this effect was inhibited by inhalation of pure oxygen. Oyarzun and Clements (1977, 1978) reported that increasing minute ventilation increases the phospholipid (surfactant) content of subsequent lung lavage fluid. As this response could be inhibited by atropine, propranolol and indomethacin, they concluded that the increase might be mediated by acetylcholine, beta-adrenergic mediators or prostaglandin. However, Nicholas and Barr (1981, 1983) could not reproduce the inhibition of surfactant release via these mechanisms, and concluded that the only proven stimulus for surfactant release is an increase in tidal volume. An alternative interpretation of our results might be that the maintenance of lung volume by PEEP encourages the regeneration of surfactant, and the restoration of normal surface tension prevents the progression to hyaline membranes. This interpretation might also be applied to the findings of Hamilton and colleagues (1983) and Pesenti and co-workers (1982).

The collapsed sections of the lung are inevitably hypoxic. Bressack and Bland (1980) studied the pulmonary vascular response to hypoxia in newborn lambs and suggested that hypoxia increased the pulmonary transvascular pressure gradient, increasing filtration of fluid into the lungs. Hypoxia may also alter local metabolic functions in the lung. O'Brodovich and associates (1981) also found an increase in the transvascular pressure gradient and an increase in endothelial permeability to all sizes of plasma proteins, particularly the larger proteins, in a model of acute respiratory failure in sheep. They detected decreased degradation of bradykinin as a result of hypoxic modification of the pulmonary converting enzyme activity and postulated that the increased concentration of bradykinin was one of the mechanisms responsible for the permeability changes.

In conclusion, we have demonstrated that the maintenance of lung volume and the prevention of collapse and re-expansion of lung units with each ventilatory cycle improves oxygenation and reduces hyaline membrane formation. Taking this in conjuction with the findings of other workers it appears that the maintenance of lung volume is the important factor, and not the pattern of ventilation itself.

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SPECIFIC ANTIBODIES TO HALOTHANE-INDUCED LIVER ANTIGENS IN HALOTHANE-ASSOCIATED HEPATITIS

J. G. KENNA, J. NEUBERGER AND R. WILLIAMS

SUMMARY

Antibodies to halothane-altered liver cell determinants (halothane antibodies) have previously been detected in serum of patients with fulminant hepatic failure after halothane anaesthesia. However, their diagnostic value has not been reported in patients with non-fulminant hepatitis. Sera from 39 patients who developed hepatitis following halothane anaesthesia between January 1983 and December 1985 were tested for antibodies to halothane-induced liver antigens using an ELISA; 22 of these patients had hepatitis without encephalopathy. Nineteen of the sera were from patients anaesthetized during 1985; four of the patients were aged 15 yr or less. All patients had undergone previous anaesthesia 17 days to 13 yr (median 3 yr) earlier. In 19 of the patients the final operation was a minor surgical procedure, lasting less than 45 min. In 13 patients a previous adverse reaction to halothane was documented in the case records. Twelve of the patients died. Halothane antibodies were detected in 12 of the 16 (75%) patients with hepatic encephalopathy and 16 of the 23 (70%) who did not develop encephalopathy, demonstrating that halothane antibodies are detectable in a wider spectrum of halothane-associated liver damage than previously appreciated.

The spectrum of liver damage that may follow halothane anaesthesia varies from the frequent, minor increases in the concentration of serum aminotransferase to the rare instances of fulminant hepatic failure (Wright et al., 1975; Pohl and Gillette, 1982; Neuberger and Williams, 1984). Previous studies have demonstrated the presence of circulating antibodies reacting with novel, halothane-induced liver cell membrane antigens (halothane antibodies) in about 70% of patients with fulminant hepatic failure following halothane (Kenna, Neuberger and Williams, 1984). Whether or not these antigens are implicated in the pathogenesis of the liver damage, demonstration of these antibodies is of diagnostic value, since these antibodies cannot be detected in the serum of patients with other forms of liver disease, in patients with no or minor abnormalities of liver function following halothane anaesthesia or in patients who, following halothane anaesthesia, have developed fulminant hepatic failure attributable to other causes (Davis et al., 1980; Vergani et al., 1980; Neuberger et al., 1983; Kenna, Neuberger and Williams, 1984). However, little is known about the incidence of these antibodies in patients with less severe reactions who do not develop encephalopathy, a group which, in some series, represents up to 75% of patients with presumed halothane hepatitis (Walton et al., 1976).

Until recently, our personal experience of halothane-associated hepatitis was largely limited to those patients, with fulminant halothane hepatitis, referred to the Liver Failure Unit for management. However, with the greater awareness of a diagnostic test for the condition, sera from patients with a wider spectrum of liver damage have been referred for testing. In this report, we describe the findings in a series of 39 patients with halothane-associated hepatitis, with and without encephalopathy, who were anaesthetized in the 3 years between 1983 and 1985.

J. G. KENNA, PH.D.; JAMES NEUBERGER,* D.M., M.R.C.P.; ROGER WILLIAMS, M.D., F.R.C.P.; The Liver Unit, King's College Hospital and School of Medicine, Denmark Hill, London SE5 9RS Accepted for Publication: March 5, 1987.

*Present address, for correspondence: The Liver Unit, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH.

TABLE I. *Pattern of referral of patients with halothane hepatitis*

Year	No. admitted to Liver Unit, KCH	No. of sera sent for halothane antibody testing
1983	3	4
1984	2	11
1985	6	13
Total	11	28

PATIENTS

Patients

Between January 1, 1983 and December 31, 1985, 11 patients were referred to the Liver Unit with otherwise unexplained hepatitis following halothane, nine had fulminant hepatic failure (table I). In addition, samples of serum from a further 28 patients, of whom only seven had fulminant hepatic failure, were sent for testing. Ninteen of the patients developed the hepatitis in 1985 (table I). In all the patients evidence of hepatic damage had appeared within 28 days of a documented halothane anaesthetic and in none was there any other known cause for the liver damage. Infection with hepatitis viruses A and B, cytomegalovirus and toxoplasma was excluded by serological testing and in no patient was there a history of alcohol excess.

Methods

Sera were tested for halothane antibodies by ELISA, as described in detail elsewhere (Kenna, Neuberger and Williams, 1984). Sera were absorbed to remove antibodies to normal liver antigens, then tested for binding to control and halothane pre-treated rabbit liver microsomal fractions which had been bound to wells of microtitre plates. Antibody binding was quantitated by incubation with peroxidase-labelled anti-human IgG, following which peroxidase activity was determined using *o*-phenylenediamine. Halothane antibodies were calculated as: $A_{490}\text{diff} = A_{490}\text{hal} - A_{490}\text{control}$ where A_{490}hal and A_{490} control represent antibody binding to the halothane altered and control rabbit liver fractions, respectively.

RESULTS

Sixteen of the 39 patients developed fulminant hepatic failure, according to the criteria of Trey and Davidson (1970). Of these, 10 progressed to grade IV encephalopathy and died from liver failure. A further two patients progressed to grade III encephalopathy and both died, one from renal failure and the other from sepsis. Of the remainder, 23 had no evidence of hepatic encephalopathy and all these survived (table II).

Six of the patients were male. Ages ranged from 1.5 to 75 yr (median 58 yr) and were similar in those with and without encephalopathy. All of the patients had received at least one previous general anaesthetic (range 1–6, median 3 in those with encephalopathy and range 1–8, median 2 in those who did not develop encephalopathy). In 22 patients, including 11 who did not develop hepatic encephalopathy, it was possible to determine that the patient had been exposed to halothane. In the remaining subjects, it was not possible to determine which anaesthetic agents had been used in the penultimate operation. The interval between the final halothane anaesthetic and the most recent previous anaesthetic ranged from 17 days to 13 yr (median 3 yr). However, the median interval between the last two anaesthetics was 6 weeks in those who developed grade III/IV encephalopathy, compared with a median of 7 yr in those with grade I/II encephalopathy and 1 yr in those who did not become encephalopathic. These differences are not statistically significant. In eight patients the interval was less than 3 months; in two of these less than 1 month. Thirteen of the patients had had a documented adverse reaction to halothane before the final exposure to the drug, and five of these developed encephalopathy. This adverse reaction consisted of jaundice in four, unexplained postoperative pyrexia in nine, and nausea, vomiting and malaise in one.

The final operation was classified as major in 14 of the patients (cholecystectomy, clipping of berry aneurysm, oesophageal fistula repair, hysterectomy, orthopaedic, mastectomy, thyroid resection, parotid gland removal or rectopexy). The remainder had undergone minor surgery (ophthalmic surgery, dilatation and curettage, hypospadias, orthopaedic, breast biopsy, cystoscopy, colonoscopy, nasal polypectomy, salivary gland surgery or varicose vein stripping). In none of the operations was there any record of major intraoperative or immediate postoperative complications.

The interval between exposure to halothane and the onset of signs of hepatic decompensation ranged from 3 to 28 days (median 8 days) and was

TABLE II. *Clinical details of patients with halothane hepatitis. Median (range) or No.* (%)

	With encephalopathy		
	Grade III/IV (*n* = 12)	Grade I/II (*n* = 4)	Without encephalopathy (*n* = 23)
Age (yr)	58 (3–75)	52 (1–75)	59 (1–68)
Sex ratio (F:M)	10:2	4:0	19:4
Type of operation (major:minor)	7:5	2:2	15:8
Previous anaesthetics	3 (1–5)	4 (3–6)	2 (1–8)
Intervals between final anaesthetics	6 wks (17 d–12 yr)	7 yr (5 mo–12yr)	1 yr (5 wk–13 yr)
Previous documented halothane reactions	3 (25%)	4 (100%)	6 (26%)
Interval, final anaesthesia to jaundice (days)	7 (1–28)	7 (7–10)	9 (1–23)
Peak AST concn (iu litre^{-1})	900 (294–3279)	828 (794–2616)	1086 (442–4000)
Survival	0 (0%)	4 (100%)	23 (100%)

TABLE III. *Halothane antibody results.* **Upper limit of normal* = *0.016* (*mean*+*3* × *SD of results obtained with 26 normal control sera*)

	With encephalopathy		
	Grade III/IV (*n* = 12)	Grade I/II (*n* = 4)	Without encephalopathy (*n* = 23)
Halothane antibodies			
Incidence	8 (67%)	4 (100%)	16 (70%)
Median A_{490} diff*	0.235	0.156	0.223
Range of A_{490} diff	(0.050–0.551)	(0.151–0.488)	(0.053–0.653)
Interval halothane exposure to testing (days)			
Median	28	29	26
Range	(4–67)	(21–49)	(11–77)

similar in those who did and did not develop encephalopathy. The interval between exposure to halothane and the taking of the serum for testing ranged from 4 to 67 days (median 20 days) and was similar in all three groups. The interval between anaesthesia and death in the 12 who died ranged from 6 to 74 days (median 28 days). In the 39 patients, the peak recorded serum AST concentration ranged from 294 to > 4000 iu litre^{-1} (median 905 iu litre^{-1}) and maximal prolongation of the prothrombin time was in the range 0–210 s (median 19 s).

The development of hepatic encephalopathy and mortality did not correlate with age, sex distribution, number of previous anaesthetics, incidence of previous adverse reactions to halothane, type of surgery (major or minor) or the interval from anaesthetic to the onset of jaundice (table II). In three patients, more than one serum sample was available and repeat testing showed no change in the presence or absence of halothane antibody.

Halothane antibodies were detected in the serum of 28 (72%) of the patients. Of the 23 without encephalopathy, antibodies were present in 16 (70%) and of those with fulminant hepatic failure, halothane antibodies were detectable in 12 (75%). The amounts of antibodies were similar in all three groups (table III).

Comparison of those patients with and without detectable concentrations of antibodies also showed that there was no difference with respect

TABLE IV. *Comparison of halothane antibody positive and negative patients. Median (range) or No.* (%). *$P < 0.05$

	Antibody positive ($n = 28$)	Antibody negative ($n = 11$)
Age (yr)	50 (1–75)	58 (3–67)
Sex ratio (F:M)	24:4	9:2
AST concn (iu litre^{-1})	950 (329–4000)	1400 (294–2436)
Incidence of encephalopathy	16 (57%)	7 (64%)
Survival	20 (71%)	8 (73%)
Previous anaesthetics	4* (1–8)	1 (1–2)
Interval halothane exposure to jaundice (days)	7 (1–28)	12 (1–23)
Interval halothane exposure to testing (days)	26 (6–67)	28 (4–37)

to age, sex ratio, proportion having major or minor surgery (as defined above), degree of liver damage as assessed by increased concentration of serum aminotransferase, the incidence of encephalopathy (57% antibody positive and 64% antibody negative) and mortality (29% antibody positive and 27% antibody negative) (table IV). There was also no difference with respect to the timing of the samples (26 days for the antibody positive patients and 28 days for the antibody negative ones). The only significant feature was that those with detectable concentrations of halothane antibodies had undergone a greater number of anaesthetics (median 4 in those with the antibody compared with median 1 in those without; $P < 0.05$, Spearman's Rank Test).

DISCUSSION

Greater awareness of the availability of a diagnostic test has resulted in our now being able to test serum from patients with a wide spectrum of otherwise unexplained liver damage following halothane anaesthesia. The results from the present study have demonstrated that the antibody is found in patients who have developed hepatitis but without encephalopathy, as well as those who have progressed to fulminant hepatic failure, and in a similar proportion of patients in both groups (approximately 70%). The spectrum of liver damage seen in this study is similar to that reported in a retrospective analysis of unexplained hepatitis following halothane between 1971 and 1973, and reported by Walton and colleagues (1976).

Halothane antibodies were not detectable in serum from about one-quarter of the patients. It is unlikely that the timing of the samples was the cause of the negative findings, since there was no difference in timing between those with and without antibody. Where repeat samples were obtained, these also were negative. It is possible that antibodies were present, but at titres too low for detection. Furthermore, antibody might be hidden by being bound in the form of antibody–antigen complexes, but disruption of circulating immune complexes, which are increased in these patients (Canalese et al., 1981), has not revealed such complexed antibodies (Kenna, unpublished data). An alternative possibility is that the antibody becomes bound onto antigen on the surface of the hepatocyte *in vivo*. We have no evidence to suggest that, in the antibody negative patients, causes other than halothane are responsible for the liver damage, although it must be emphasized that the diagnosis of halothane-associated hepatitis remains, especially in the absence of detectable halothane antibodies, largely one of exclusion, and it may be that some of the cases are attributable to the non-A non-B hepatitis viruses for which there are no serological markers, or from other causes. While demonstration of the halothane antibody provides confirmation of the cause of the liver damage, failure to demonstrate the antibody does not preclude the diagnosis. A similar analogy is myasthenia gravis, in which the presumed pathogenetic autoantibodies are detectable in a similar proportion of patients (Lindstrum et al., 1976). In only 22 of the patients was it possible to show that the subject had had more than one exposure to halothane. While it may be that halothane-associated hepatitis may follow a first exposure to the agent, it must be emphasized that halothane was and, quite rightly, remains a frequently used anaesthetic so that it is possible that the previous anaesthetic agent was halothane. Furthermore, recent evidence suggests that enough halothane may be absorbed onto the tubing in the anaesthetic circuitry to sensitize a patient given a "non halothane" anaesthetic (Varma, Whitesell and Iskandarani, 1985).

As in other studies, the patients were predominantly middle aged and female, and all had undergone previous anaesthesia. The outcome and severity of the liver damage showed no significant correlation with the number of previous anaesthetics or the interval between the final two anaesthetics. In particular, there was a wide range of intervals between the final two anaesthetics, ranging up to 12 yr in those who developed encephalopathy and up to 11 yr in those without encephalopathy; thus there appears to be no "safe interval" beyond which repeat exposure to halothane will not result in liver damage. Furthermore, these findings do not support the suggestion that a short interval between halothane exposures is associated with more severe liver damage.

It is clear that cases of halothane-associated hepatitis continue to occur in the U.K., although little can be deduced about the annual incidence because of the uncertainty concerning rates of referral. However, the number of presumed cases referred to us is greater than that referred to the Committee on Safety of Medicines (Committee on Safety of Medicines, personal communication). It is disturbing to note that in one-third of these patients, there had been a documented previous adverse reaction following halothane. This suggests that, if a full history had been available before the final anaesthetic, a potentially fatal complication might have been avoided.

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REPRODUCTIVE AND TERATOGENIC EFFECTS OF NITROUS OXIDE, FENTANYL AND THEIR COMBINATION IN SPRAGUE–DAWLEY RATS

R. I. MAZZE, M. FUJINAGA AND J. M. BADEN

SUMMARY

The reproductive and teratogenic effects of 35% and 50% nitrous oxide, fentanyl 500 µg kg⁻¹/day and their combinations were studied using a total of 419 timed-pregnant Sprague–Dawley rats. On day 7 of pregnancy, osmotic minipumps which delivered either fentanyl 500 µg kg⁻¹/day or normal saline for 2 weeks were implanted subcutaneously in the back of the rats. Animals then were exposed to air, 35% nitrous oxide or 50% nitrous oxide for 24 h on day 9 of pregnancy. On day 21 of pregnancy, Caesarean sections were performed and all 2693 offspring were preserved and subsequently examined microscopically for external, visceral and skeletal abnormalities. There were no reproductive or teratogenic effects observed with 35% nitrous oxide, but adverse effects were observed with 50% nitrous oxide. The addition of fentanyl to the nitrous oxide increased the mortality rate among the rats, but did not significantly add to the adverse reproductive or teratogenic effects of nitrous oxide.

The administration of 75% nitrous oxide to Sprague–Dawley rats for 24 h on day 9 of pregnancy results in adverse reproductive and teratogenic effects (Fink, Shepard and Blandau, 1967; Lane et al., 1980; Mazze et al., 1984; Keeling et al., 1986). However, the minimum toxic concentration of nitrous oxide administered for 24 h on day 9 is unknown although, in a previous investigation (Mazze et al., 1986), we showed that 25% nitrous oxide was devoid of adverse effects. It is unknown also whether the administration of other central nervous system depressant drugs in combination with nitrous oxide, as is practised in clinical anaesthesia, would increase its reproductive toxicity. The present study was designed to answer these questions. Our first goal was to determine the threshold of reproductive toxicity of nitrous oxide in Sprague–Dawley rats; our next was to determine whether fentanyl, in combination with the nitrous oxide, altered this threshold.

MATERIALS AND METHODS

Three separate studies were performed utilizing the same design (table I). A total of 419 timed-pregnant Sprague–Dawley rats were obtained from the breeder (Hilltop Lab Animals, Inc., Scottdale, Pennsylvania 15683) on day 6 of pregnancy and individually labelled with metal ear tags. (The day a plug was observed in the vagina was defined as day 1 of pregnancy.) Rats were weighed on arrival and assigned to six groups of approximately equal average weight (table II). They were bedded on ground corncob, housed four per cage and fed standard laboratory rodent food and tap water *ad libitum*. Temperature in the animal room was maintained at 21–24 °C and artificial light was provided from 6 a.m. to 7 p.m. each day.

On day 7 of pregnancy, osmotic minipumps (Alzet mini-osmotic pump; Alza Corporation, Palo Alto, California 94304) were implanted subcutaneously in the back of the rats under general anaesthesia obtained with an i.m. injection of 0.3 ml kg⁻¹ of a mixture containing ketamine 60 mg ml⁻¹, xylazine 6 mg ml⁻¹ and acepromazine 1.2 mg ml⁻¹. The osmotic minipump is a self-powered pump which utilizes osmotic pressure to

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RICHARD I. MAZZE, M.D.; MASAHIKO FUJINAGA, M.D.; JEFFREY M. BADEN, M.B., B.S., F.F.A.R.C.S., M.R.C.P.; Department of Anesthesia, Stanford University School of Medicine, Stanford, California 94305, U.S.A. and Anesthesiology Service, Palo Alto V.A. Medical Center, Palo Alto, California 94304, U.S.A. Accepted for Publication: April 1, 1987.

TABLE I. *Numbers of rats studied in each group in the three separate investigations. Fentanyl 500 µg kg^{-1}/day (Fent.) was administered by osmotic minipump continuously from day 7 to day 21 of pregnancy. Nitrous oxide was administered for 24 h on day 9 of pregnancy*

	Group 1 Control	Group 2 Fent.	Group 3 35%N_2O	Group 4 35%N_2O +Fent.	Group 5 50%N_2O	Group 6 50%N_2O +Fent.	Total
Study I	40	30	30	30	—	—	130
Study II	40	30	—	—	30	30	130
Study III	34	—	24	33	24	44	159
Total	114	60	54	63	54	74	419

deliver its contents continuously and at a constant rate (Theeuwes and Yum, 1976). We used model 2002 which is 3.0 cm long by 0.7 cm in diameter and delivers 1 µl h^{-1} for 2 weeks. The total daily dose of fentanyl, 500 µg kg^{-1}, was based on the average starting dam weight of 212 g. To achieve this dose, a 0.44% solution of fentanyl was prepared from fentanyl–citrate powder (Janssen Pharmaceutica, Inc., 40 Kingsbridge Road, Piscataway, New Jersey 08854) dissolved in normal saline. For the control and nitrous oxide alone groups, the pumps were filled with physiological saline.

On day 9 of pregnancy, nitrous oxide was administered to the rats which were in gas-tight, Plexiglas chambers of approximately 1000-litre capacity. They were placed in the chambers in their cages without food or water. Medical grade nitrous oxide and oxygen were delivered to the chambers and were mixed with room air to achieve the desired nitrous oxide and oxygen concentrations. Rats in the control and fentanyl alone groups were exposed to room air simultaneously in another chamber. Nitrous oxide concentrations were monitored continuously with Miran 1A–1F infra-red analysers and were recorded on strip-chart recorders; they were maintained within 5% of the desired value. Oxygen concentration was monitored continuously with IL402 analysers and was maintained at 22–25%. Exposure was started at 9 a.m. on day 9 of pregnancy and continued until 9 a.m. on day 10 of pregnancy. All rats were weighed before and after exposure and every 2–4 days during the study. Rats that died during exposure to nitrous oxide were subjected to limited autopsy to determine if they were pregnant.

On day 21 of pregnancy, 1 day before delivery was expected, rats were sacrificed by carbon dioxide inhalation and Caesarean sections were performed. The uterus was examined and the number and position of live and dead fetuses, resorptions and implantations were recorded. The weight and sex of each live fetus were determined and each fetus was examined for external abnormalities. Every other fetus was fixed in 70% ethanol and macerated with potassium hydroxide. The skeleton was then stained with alizarin red S using the modified method of Staples and Schnell (1964), cleared with glycerol and subsequently examined microscopically for skeletal abnormalities. The remainder of the fetuses were preserved in Bouin's solution and subsequently dissected and examined microscopically for visceral abnormalities as described by Barrow and Taylor (1967). All examinations were made without knowledge of the treatment group.

Abnormalities were classified as follows. Fetal morphological abnormalities that altered general body conformation, disrupted or interfered with bodily functions, or generally were incompatible with life were categorized as major malformations. Abnormalities in anatomical structure that were considered to have no significant biological effects on the rats' health or on their body conformity and represented only slight deviations from normal were categorized as developmental variants. Abnormalities which were not within the strict definition of major malformations, but which clearly were not developmental variants, were categorized as minor anomalies. Fetuses weighing 25% less than the mean weight of their litter were classified as runts.

Statistical analyses

The percentage of fetuses affected in each litter was computed for each type of abnormality. Data were analysed by chi-square analysis and by analysis of variance (ANOVA). Student's *t* test, corrected for multiple analysis, was used as an

TABLE II. *Numbers of rats that died during the investigation, body weight and changes in body weight (mean ± SD).* *P < 0.05 v. *control by Student's* t *test. The day a plug was observed in the vagina was defined as day 1 of pregnancy. Fentanyl 500 μg kg*$^{-1}$*/day (Fent.) was administered by osmotic minipump continuously from day 7 to day 21 of pregnancy. Nitrous oxide was administered for 24 h on day 9 of pregnancy*

	Group 1 Control	Group 2 Fent.	Group 3 35%N_2O	Group 4 35%N_2O +Fent.	Group 5 50%N_2O	Group 6 50%N_2O +Fent.
No. of rats initially studied	114	60	54	63	54	74
No. of rats that died after pump implantation	0	0	0	3	0	0
No. of rats that died during N_2O exposure	0	1	0	10	0	41
Weight (g)						
On arrival (day 6 of pregnancy)	213±3	213±3	212±2	212±2	212±2	212±3
Weight loss during the exposure	23±3	27*±3	24±5	30*±5	29*±6	32*±5
At Caesarean section (day 21 of pregnancy)	351±32	342±29	357±23	347±30	321*±26	308*±28
Weight gain during the experiment (day 21–day 6)	135±23	129±21	139±15	127±27	106*±23	96*±29

a posteriori test when differences were found with ANOVA. $P < 0.05$ was considered statistically significant.

RESULTS

The results of the three studies were combined, since the design of the studies was identical and, when analysed separately, there were no differences in any of the variables among the three control groups.

Maternal effects

Three group 4 rats (35% nitrous oxide + fentanyl) died within 24 h after implantation of the pump (table II). Rats exposed to 35% and 50% nitrous oxide appeared only mildly sedated. They rested quietly during most of the exposure, occasionally changing their posture and walking about the cage. Rats exposed to the combined treatment, particularly 50% nitrous oxide plus fentanyl, were more sedated. They appeared to sleep during most of the exposure and changed position only infrequently. One rat in group 2 (fentanyl), 10 rats in group 4 and 41 rats in group 6 (50% nitrous oxide + fentanyl) died during the period of exposure. Weight loss during the 24-h exposure was significantly greater than control in all of the fentanyl treated rats (groups 2, 4 and 6) and in the 50% nitrous oxide group (group 5). However, body weight on day 21 of pregnancy and total weight gain during the investigation were significantly less than control only in rats from groups 5 and 6 (table II).

Reproductive effects

There were no differences in the overall rate of pregnancy and in the total number of implantations among all the groups (table III). However, the total number of live fetuses per rat was significantly less, and the total number of resorptions per rat and the post-implantation fetal loss were significantly more in groups 5 and 6 rats than in the control group (group 1). The pregnancy rate among rats examined at Caesarean section was significantly less in group 6 than in the control group.

Teratogenic effects

A total of 2693 offspring were delivered and all were examined for external abnormalities. Subsequently, 1346 fetuses were examined for visceral and 1347 for skeletal abnormalities. The results of fetal examinations are shown in table IV. There were no significant increases in external abnormalities in any of the groups. The incidence of major and minor visceral abnormalities and of minor skeletal anomalies were increased in groups 5 and

TABLE III. *Reproductive indices (mean ± SD).* *$P < 0.05$ v. *control by Student's* t *test*; †$P < 0.05$ v. *control by* χ^2 *test.* #*Including rats that died before Caesarean section*; ‡*including those rats which died during exposure*; ††*including rats initially studied, less those that died following fentanyl pump implantations and nitrous oxide exposure.* §[(*Total No. Implantations – Total No. Live fetuses*)/*Total No. Implantations*] × 100. *Fentanyl 500 μg kg*$^{-1}$/*day (Fent.) was administered by osmotic minipump continuously from day 7 to day 21 of pregnancy. Nitrous oxide was administered for 24 h on day 9 of pregnancy*

	Group 1 Control	Group 2 Fent.	Group 3 35%N_2O	Group 4 35%N_2O + Fent.	Group 5 50%N_2O	Group 6 50%N_2O + Fent.
No. of rats studied	114	60	54	63	54	74
No. of rats pregnant‡	85	47	41	40	41	49
Overall pregnancy rate# (%)	75	78	76	64	76	66
Caesarean section						
No. of rats examined††	114	59	54	50	54	33
No. of rats pregnant	85	47	41	32	41	16
Pregnancy rate among examined rats (%)	75	80	76	64	76	48†
Total implantations/rat	11.8±2.5	11.5±2.9	12.3±1.7	12.6±1.8	11.7±2.0	10.7±2.6
Total live fetuses/rat	11.2±3.0	10.9±3.1	11.6±1.7	10.9±3.3	7.7*±3.5	6.4*±4.2
Total resorptions/rat	0.5±1.0	0.6±0.9	0.6±0.9	1.2±1.5	4.1*±3.5	3.9*±3.4
Post-implantation loss/rat (%) §	5.8±14.6	5.8±10.2	5.4±7.6	13.4±23.9	34.0*±28.1	43.0*±34.1
Mean fetal body weight (g)	4.5±0.4	4.5±0.4	4.5±0.3	4.3±0.4	3.9±0.4	3.9±0.8
Female fetuses/rat (%)	50.9±15.0	47.0±17.1	49.2±12.6	52.1±14.9	51.7±20.2	53.5±26.2

TABLE IV. *Summary of fetal examinations (mean per cent abnormal fetuses per rat ± SD).* *$P < 0.05$ v. *control by Student's* t *test.* †*Includes only those rats which had live fetuses. Fentanyl 500 μg kg*$^{-1}$/*day was administered by osmotic minipump continuously from day 7 to day 21 of pregnancy. Nitrous oxide was administered for 24 h on day 9 of pregnancy*

	Group 1 Control	Group 2 Fent.	Group 3 35%N_2O	Group 4 35%N_2O + Fent.	Group 5 50%N_2O	Group 6 50%N_2O + Fent.
No. of rats examined†	84	47	41	30	39	15
External examinations						
No. of fetuses examined	954	510	479	342	306	102
Major malformations	0.0±0.0	0.1±1.0	0.4±1.6	1.2±5.2	0.8±3.4	1.1±4.4
Minor anomalies	0.3±1.8	0.4±1.9	0.4±1.6	1.2±5.2	0.6±2.5	1.1±4.4
Runt	0.6±2.2	0.2±1.3	0.7±2.6	0.9±3.9	1.3±4.6	1.1±4.4
Visceral examinations						
No. of fetuses examined	474	256	241	171	153	51
Major malformations	0.0±0.0	0.0±0.0	0.3±2.2	0.7±3.7	6.1*±17.7	15.7*±30.3
Minor anomalies	4.7±8.9	4.6±9.7	6.3±10.3	8.5±13.7	17.8*±29.0	20.9*±29.3
Developmental variants	1.2±10.9	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0	0.0±0.0
Skeletal examinations						
No. of fetuses examined	480	254	238	171	153	51
Major malformations	0.0±0.0	0.0±0.0	0.4±2.7	1.7±9.1	1.1±4.8	0.0±0.0
Minor anomalies	0.6±3.0	2.2±14.7	0.8±3.5	1.1±4.3	7.6*±14.3	9.5*±27.5
Developmental variants	29.0±25.1	21.1±25.8	41.9±27.7	58.2*±31.7	35.8±28.2	68.3*±33.9

6 rats, but the differences between the two groups were not significant. Similarly, there were increases in minor skeletal anomalies in rats in groups 5 and 6. Skeletal development variants were increased in groups 4 and 6 (combined treatment), but not in the corresponding nitrous oxide alone groups. The difference between groups 5 and 6 was statistically significant.

DISCUSSION

In 1967, Fink, Shepard and Blandau first reported that nitrous oxide was teratogenic in rats. Later, the same group (Shepard and Fink, 1968) exposed Sprague–Dawley rats to 70% nitrous oxide for 24 h on various days of pregnancy and noted that the incidence of skeletal malformations was highest after exposure on days 8–10 of pregnancy. These results were confirmed by Lane and colleagues (1980) who exposed Sprague–Dawley rats, for 24 h on day 9 of pregnancy, to 70–75 % concentrations of nitrous oxide, nitrogen or xenon in oxygen, or to room air. Only treatment with nitrous oxide led to an increase in the incidence of resorptions and major soft tissue and skeletal anomalies. Xenon is a slightly more potent anaesthetic than nitrous oxide. The fact that it did not cause teratogenic effects suggests that the results with nitrous oxide are drug-specific and are not related to the properties of anaesthetics in general. In our laboratory, we exposed Sprague–Dawley rats to 0.75 %, 7.5 %, 25 % and 75 % nitrous oxide for 24 h on day 9 of pregnancy and found significant increases in the incidences of resorptions and structural abnormalities with 75 % nitrous oxide, but not with 25 % nitrous oxide or less (Mazze et al., 1984). Similarly, Keeling and co-workers (1986) noted an increased incidence of skeletal malformations in Sprague–Dawley rats exposed to 70–75 % nitrous oxide on day 9 of pregnancy. They also reported that pretreatment with folinic acid partially reduced the teratogenic effects of nitrous oxide.

From these studies it is clear that 75 % nitrous oxide causes adverse reproductive effects when administered for 24 h on day 9 of pregnancy. However, until the present study, the minimum toxic concentration of nitrous oxide has not been known. We now have this information: 35 % nitrous oxide is not associated with adverse reproductive effects when administered for 24 h on day 9 of pregnancy, but 50 % nitrous oxide causes increased fetal loss, major and minor visceral malformations and minor skeletal anomalies.

Given this information, we could then determine whether the combination of nitrous oxide and another central nervous system depressant drug, fentanyl, altered the threshold of reproductive toxicity of nitrous oxide. In a previous study (Fujinaga, Stevenson and Mazze, 1986), we administered fentanyl either 10 or 100 μg kg^{-1}/day to Sprague–Dawley rats throughout pregnancy or 500 μg kg^{-1}/day on days 3–17 of pregnancy using chronically implanted, subcutaneous, osmotic minipumps. The 500-μg kg^{-1}/day dose was associated with plasma fentanyl concentrations of 8.5 ng ml^{-1} (clinical therapeutic range: 0.5–2.5 ng ml^{-1} in general surgery (McQuay et al., 1979); 5–10 ng ml^{-1} in cardiac surgery (Bovill and Sebel, 1980)) and was the largest dose we could administer with osmotic minipumps without producing respiratory depression. In our study, no adverse reproductive effects were observed with any dose of fentanyl. Single daily bolus doses of fentanyl 100 μg kg^{-1} administered s.c. caused significant respiratory acidosis so the use of osmotic minipumps permitted administration of larger doses than would otherwise have been possible (R. I. Mazze and M. Fujinaga, unpublished observation). They also obviated the need for daily drug injections—a traumatic procedure, and a potentially confounding factor in teratology experiments.

In the present study, the administration of nitrous oxide on day 9 of pregnancy caused significant maternal toxicity in the combined treatment groups as demonstrated by a 14 % intra-anaesthetic mortality rate for the 35 % nitrous oxide + fentanyl group and a 55 % mortality rate for the 50 % nitrous oxide + fentanyl group (table II). There were no intra-anaesthetic deaths in the rats treated with nitrous oxide alone. Thus, the combined treatments clearly were stressful and, in fact, the 50 % nitrous oxide + fentanyl dose was slightly greater than the LD_{50}. In spite of this, there was only one developmental effect which could be attributed to the combined treatment that was not seen in either of the groups of rats treated with nitrous oxide alone, that is, an increased incidence of skeletal developmental variants in both nitrous oxide + fentanyl groups (table IV). The significance of developmental variants in teratology studies has been examined by Lansdown and associates (1976) who administered halothane to Sprague–Dawley rats, and by Kimmel and Wilson (1973). These authors concluded that developmental variants generally should not be considered malformations. In the latter study, only extra 14th ribs (not seen in our study) were indicators of teratogenic potential and, at that, only when the test drug was administered in a greater dose than that which caused the developmental variants. Other developmental variants were not reliable signs of teratogenic potential, although they may indicate other developmental abnormalities, such as intrauterine growth retardation. Thus our results suggest that the addition of fentanyl to nitrous oxide does not lead to an increased incidence of biologically significant anatomical abnormalities.

The only other toxic reproductive effect seen in a combined treatment group, which was not present in the corresponding nitrous oxide alone group, was the decreased pregnancy rate among 50% nitrous oxide+fentanyl treated rats examined at Caesarean section (table III). Only 48% of these rats were pregnant, compared with 76% of rats treated with 50% nitrous oxide and 75% of control rats. We cannot adequately explain this finding. Implantation of the rat embryo occurs on day 5–6, that is, before there was any intervention in the present study. Had fetal loss occurred secondary to pump implantation on day 7, all fentanyl groups should have been equally affected; this did not occur. Alternatively, if the rats in group 6 were pregnant and the fetuses died at the time of nitrous oxide exposure on day 9, there should have been evidence of this at the time of Caesarean section on day 21. There was an increased incidence of early resorptions in group 6 rats compared with control animals, but this incidence was the same as in rats treated with 50% nitrous oxide alone (group 5) having a higher pregnancy rate. Finally, it is possible, although unlikely, that there were increased fetal deaths in group 6 rats at the time of exposure and complete resorption of the fetuses occurred by day 21 when examinations were performed. All of these findings are not internally consistent, so we can do no more than report the observation.

The clinical significance of this study remains to be considered. Nitrous oxide is rarely administered alone, rather it is usually combined with other inhaled or i.v. anaesthetics. For that reason, we administered fentanyl with nitrous oxide at concentrations that were just above (50%) and just below (35%) the threshold value of reproductive toxicity in Sprague–Dawley rats. Combined treatment did not alter this threshold value. Other investigators have considered this problem and have administered nitrous oxide in combination with halothane. For example, Bussard and colleagues (1974) administered 60% nitrous oxide with 0.6% halothane to pregnant hamsters and found an increased incidence of resorptions and decreased fetal weight. Coate, Kapp and Lewis, (1979) administered several combinations of nitrous oxide and halothane to Sprague–Dawley rats and observed decreased fertility in treated animals compared with controls. However, in both of these studies the effects of treatment with nitrous oxide alone and with halothane alone were not considered separately, so it is not possible to determine if additive toxicity occurred. Pope and co-workers (1978) administered 1–50% nitrous oxide alone, 0.16–0.32% halothane alone and the combination of 10% nitrous oxide and 0.16% halothane to Sprague–Dawley rats for 8 h per day throughout pregnancy. They observed slight growth retardation as a consequence of the combined treatment, but there were no significant teratogenic or toxic reproductive interactions of the two drugs. We designed our study to detect additive toxicity if any were present, but we observed none.

Extrapolation of the results of this study to clinical practice, as with the results of any animal toxicity study, should be done with caution. With that caveat in mind, we conclude that the administration of fentanyl with nitrous oxide does not carry with it any liability for adverse reproductive effects above that which may be attributed to the administration of nitrous oxide alone. The latter treatment has never clearly been established to cause adverse reproductive effects in humans (Mazze, 1986; Crawford and Lewis, 1986).

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HIGH FREQUENCY JET VENTILATION: THE INFLUENCE OF GAS FLOW, INSPIRATION TIME AND VENTILATORY FREQUENCY ON GAS TRANSPORT IN HEALTHY ANAESTHETIZED DOGS

A. J. G. SPOELSTRA AND T. J. A. TAMSMA

Jet ventilation was introduced by Sanders (1967) to improve gas exchange during ENT procedures. Oberg and Sjostrand (1971) also used jet ventilation during research on the carotid sinus reflex, but increased the applied frequency. It was not until 1982 that the several forms of high frequency ventilation were defined clearly (Gallagher, Klain and Carlon, 1982).

Although simple catheters or transtracheal needles (Klain and Smith, 1977) were used initially, special connectors with an injector (Carlon et al., 1981) and a multilumen tracheal jet tube were developed later (Babinski et al., 1983).

Several workers showed that high frequency jet ventilation (HFJV) can be an alternative to intermittent or continuous positive pressure ventilation (IPPV, CPPV). Application of HFJV, however, has been a matter of trial and error with respect to the setting of the ventilator variables. Moreover, studies that have been undertaken are often difficult to compare, since the ventilators and the experimental or clinical settings were totally different. Consequently, there is no understanding of all the factors essential for efficient HFJV. We have, therefore, studied the influence of factors such as gas flow, inspiration time (as a percentage of the total ventilatory cycle) and frequency on gas exchange and cardiac output during HFJV in healthy anaesthetized dogs.

SUMMARY

High frequency jet ventilation (HFJV) experiments were performed in healthy anaesthetized mongrel dogs via a multilumen tracheal jet tube to examine the influence of gas flow, ventilatory frequency and inspiration time (as a percentage of the total ventilatory cycle) on gas exchange. We compared arterial P_{O_2}, P_{CO_2} *and cardiac output during periods of adequate intermittent positive pressure ventilation (IPPV) and periods of HFJV. Reducing gas flow by decreasing the number of activated valves and increasing the frequency to greater than 4 Hz resulted in less than optimal arterial* P_{O_2} *and* P_{CO_2} *compared with IPPV. This indicates that convection during HFJV is probably essential for efficient gas exchange. Inspiration time proved to be important in determining efficacy of ventilation for a fixed ventilator minute volume. Cardiac output during all HFJV settings was equal to or greater than cardiac output during IPPV, even at those HFJV settings that resulted in a positive end-expiratory pressure.*

SUBJECTS AND METHODS

Anaesthesia was induced in healthy mongrel dogs (weight 15–20 kg) with sodium thiopentone and maintained with a constant infusion of a mixture of droperidol 0.5 mg kg^{-1} h^{-1}, methadone 0.3 mg $kg^{-1}h^{-1}$, atropine 0.015 mg kg^{-1} h^{-1} and pancuronium bromide 0.1 mg kg^{-1} h^{-1} (De Vries, 1976).

The trachea was intubated and the lungs ventilated with a Siemens Elema 900B Servo ventilator using a mixture of oxygen and air ($F_{I_{O_2}}$ = 0.3). Tidal volume was adjusted to obtain an

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A. J. G. SPOELSTRA, M.D., PH.D., Laboratory for Physiology, Free University, v.d. Boechorststraat 7, 1081 BT Amsterdam, The Netherlands. T. J. A. TAMSMA, M.D., Department of Anaesthesiology, Academic Hospital, Free University, P.O. Box 7057, 1007 MB Amsterdam, The Netherlands. Accepted for Publication: October 2, 1986.

end-tidal $P\text{CO}_2$ ($P\text{E}'_{\text{CO}_2}$) of about 5 kPa (measured using a Siemens capnograph) at a fixed ventilation frequency of 12 b.p.m.

Pulmonary artery pressure (PAP), central venous pressure (CVP) and cardiac output were measured via a 7-French gauge pulmonary artery thermodilution catheter. Systemic arterial pressure (SAP) was measured via a catheter introduced to the femoral artery. PAP and SAP were measured by Gould Statham P23ID pressure transducers. CVP was measured with a Datascope PT10 pressure transducer. Cardiac output was obtained by thermodilution (Edwards 9520A cardiac output computer; average of three injections at end-expiration, heparinized saline 5 ml at ambient temperature). The dogs received a total of 2–3 ml kg^{-1} h^{-1} of fluid i.v. A balloon catheter was introduced to the middle one-third of the oesophagus to measure oesophageal pressure (P_{oe}), while airway pressure (P_{aw}) was measured via the tube, using Validyne MP245 pressure transducers. Arterial blood-gas tensions (Pa_{O_2}, Pa_{CO_2}) were measured in heparinized blood samples with a Radiometer ABL1 analyser. HFJV was performed with a Siemens–Elema Experimental HFJV unit coupled to the gas mixer of the Servo ventilator and using the same gas mixture. The HFJV unit consists of an electronic control unit and a valve unit. The electronic unit delivers impulses to the solenoids of the valve unit. The impulses are preset with function selectors. The valve unit consists of 15 valves, mounted in five groups with three valves in each group. The valves are mounted parallel in each group and the groups are connected in parallel to the ventilation gas outlet. Each group has its own gas supply from the driving gas manifold. Valves 1–4 are connected electronically and controlled with function selector 1 on the electronic unit. Valves 5–15 are connected separately and controlled with function selectors 2–12 on the electronic unit. Fluctuations in driving gas pressure were diminished by a capacitor placed just before the valve unit. Jet nozzle size and jet location in the airway were kept constant using a Hi-Lo jet tracheal tube (NCC Mallinckrodt). The output of the valve unit was connected to the transparent connecting tube for insufflation which ended about 6 cm before the bevelled tip of the tracheal tube. This integral insufflation lumen permits the delivery of an intermittent jet ventilation into the trachea. The opaque white connecting tube which ends near the bevelled tip of the tracheal tube was used for monitoring P_{aw}. During high frequency ventilation, the tracheal tube was disconnected from the Servo ventilator and opened to air. Figure 1 shows a schematic impression of the electromechanically controlled HFJV system.

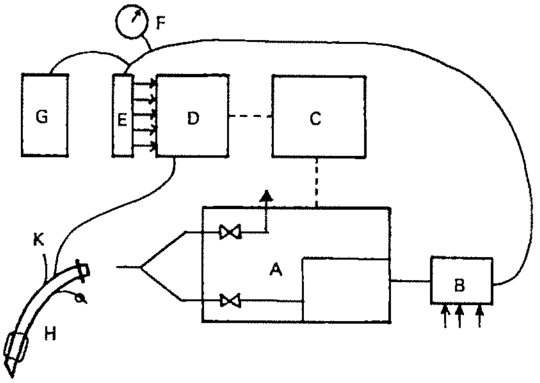

FIG. 1. Schematic representation of the HFJV system. A = Servo ventilator 900B; B = mixer; C = HFV control unit; D = valve unit; E = gas manifold; F = driving pressure manometer; G = capacitor; H = Hi-Lo jet tracheal tube; K = airway pressure connection. Connections: solid lines = gas connections; dashed lines = electronic connections.

When the surgical preparation was complete, the dog was placed in the prone position and lung compliance was restored by a few forced ventilations. The investigation was started with normal IPPV delivered by the Servo ventilator. Different settings of the function selectors were chosen randomly during periods of HFJV to investigate the influence of frequency, gas flow (valve setting) and inspiration time percentage (I.(I+E)$^{-1}$) (duty cycle), on the efficiency of this form of ventilation. To prevent interference in blood-gas tensions from previous HFJV periods, each period of HFJV was applied after a period of adequate IPPV. Blood-gas tensions were measured 10 min after the start of a new period of HFJV. Cardiac output was measured in the first 1 min after switching to and 10 min after the start of a new period of HFJV. During IPPV periods, these measurements were performed when $P\text{E}'_{\text{CO}_2}$ returned to normal. PAP, SAP, CVP, P_{oe} P_{aw} and the flow signal from the Servo ventilator were recorded on a Siemens–Elema Mingograph 804.

The HFJV minute volume was determined as follows. The rectangular gas flow delivered by the HFJV unit was led via the jet insufflation lumen of the Hi-Lo tracheal tube into a wet spirometer. The proximal end of the tracheal tube was closed to prevent air entrainment. For each valve setting up to 8, the minute volume was determined for the frequencies 1, 2, 4, 8 and 16 Hz at duty cycles 10–90 % with 10 % increments. Little was gained in minute volume by extending the valve setting to 12.

The measurements of HFJV minute volume without entrainment were performed by closing one side of the T-piece connector to avoid entrainment of air, and were compared with experimental measurements with entrainment. The total exhaled minute volume from the tracheal tube was led into a wet spirometer via a non-rebreathing double-valved T-piece connector which allowed entrainment of room air during insufflation.

Since the composition of the gas mixture influenced minute volume, we used a mixture of oxygen and air with $FI_{O_2} = 0.3$ in all experiments.

The procedure consisted of four series of experiments:

Series 1. Determination of HFJV unit minute volume.

Series 2. Seven dogs were ventilated with HFJV at a fixed frequency of 4 Hz. Duty cycle was altered at random from 20 to 40, 60 and 80 % at valve settings 2 and 8. Each combination of duty cycle and valve setting was alternated with a period of IPPV as described before.

Series 3. Seven dogs were ventilated with HFJV altering the frequency at random from 1 to 2, 4, 8 and 16 Hz, with valve settings 2 and 8, and keeping the duty cycle at 40 %. Each combination of frequency and valve setting was alternated with IPPV as described before.

Series 4. From the minute volume plot, determined in series 1, experimental settings were chosen, giving the same minute volume at different duty cycles and valve settings. At a frequency of 4 Hz, the settings were used during HFJV in seven dogs. By means of a one-way valve connected to the tracheal tube, entrainment during insufflation was prevented, repeating the HFJV sequences. Again each HFJV setting was alternated with IPPV.

Results are expressed as mean ± SEM. Statistical analysis used Student's t test for paired data. Statistical significant difference was assumed at $P < 0.05$.

RESULTS

Series 1 showed that changes in frequency did not influence minute volume, which is dependent on the rectangular form of the flow curve. A representative plot of minute volume and valve setting for 4 Hz is given in figure 2, which clearly shows the high minute volumes delivered by a high frequency jet ventilator as already indicated by Carlon and colleagues (1983). There was non-linearity in minute volume with increasing duty cycle and valve setting. This was caused by the fact that duty cycle as well as valve setting influenced driving pressure to some extent. Table I presents the relation between driving pressure, valve setting and duty cycle. The results indicate that the capacitor used was not large enough to maintain a constant driving pressure for all HFJV settings.

The results for Pa_{O_2}, Pa_{CO_2} and cardiac output from series 2, 3 and 4 are presented as percentage change from the mean of the baseline IPPV values before and after the particular HFJV period. Table II and figure 3 summarize the results of series 2 ($n = 7$). During the whole experimental period of about 6 h, baseline IPPV values for Pa_{O_2}, Pa_{CO_2} and cardiac output were, respectively:

TABLE I. *Driving pressure at different combinations of inspiration time percentage (duty cycle) (y-axis) and valve setting (x-axis)*

Duty cycle (%)	Driving pressure (kPa)							
90	173	162	152	143	136	131	128	123
80	181	168	158	150	144	138	134	131
70	188	176	168	161	154	148	143	140
60	195	185	175	168	163	158	154	150
50	202	193	185	178	173	168	165	163
40	210	202	198	191	185	182	176	175
30	216	210	205	200	197	194	193	190
20	223	220	215	212	210	206	202	200
10	230	222	225	224	222	220	220	220
Valve setting :	1	2	3	4	5	6	7	8

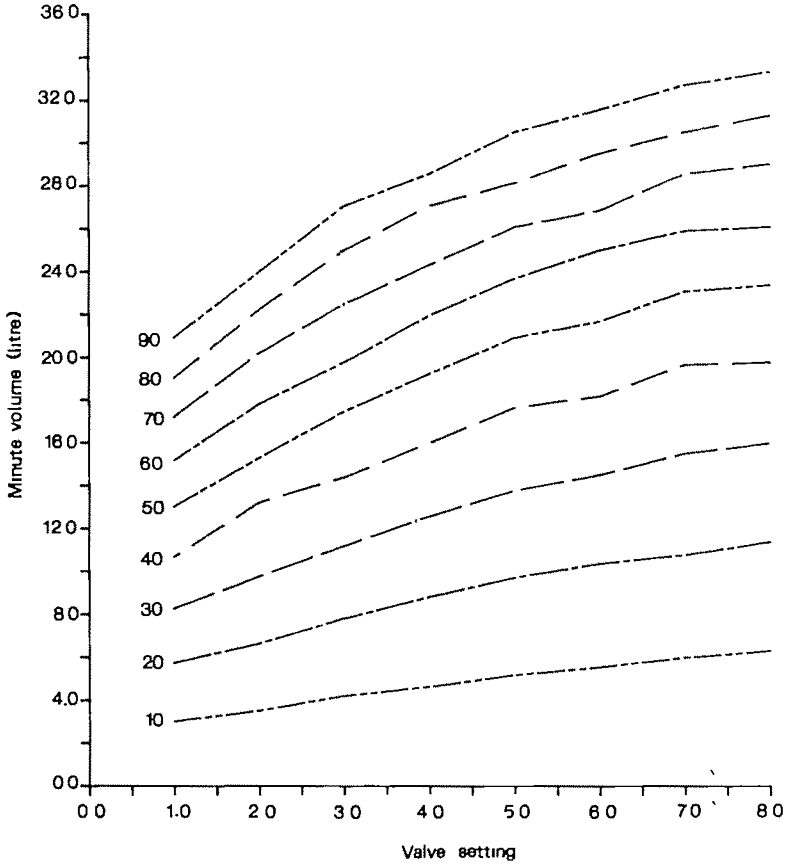

FIG. 2. Graphic representation of minute volume delivered by the HFV unit at 4 Hz and a mixture of oxygen and air ($F_{I_{O_2}} = 0.3$) related to duty cycle (range 10–90 %) and valve setting.

21.52 ± 0.23 kPa, 5.07 ± 0.11 kPa and 2.90 ± 0.31 litre min^{-1}, with a ventilation minute volume of 3.33 ± 0.25 litre min^{-1}. Blood-gas values indicate that gas exchange was maximal at 40 % duty cycle. Despite the increase in minute volume, longer inspiration time percentages resulted in reduced Pa_{O_2} and increased Pa_{CO_2}.

As shown in table II, increasing the duty cycle resulted in an increase in mean P_{oe}, mean P_{aw} and end-expiratory pressure. Ventilation minute volume (MV) and tidal volume (V_T) increased with duty cycle. Cardiac output was increased for all HFJV settings used (fig. 3), even for those settings at which Pa_{CO_2} was less than during IPPV.

TABLE II. *Results of series 2 (mean ± SEM). Valve settings (VS) 2 and 8 for each of four duty cycle (DC) values.* P_{oe} = *Oesophageal pressure*; P_{aw} = *airway pressure*; *EEP = end-expiratory pressure*; *MV = ventilation minute volume*; V_T = *tidal volume*

	DC 20 %		DC 40 %		DC 60 %		DC 80 %	
	VS 2	VS 8	VS 2	VS 8	VS 2	VS 8	VS 2	VS 8
P_{oe} (kPa)	−0.16 ± 0.04	−0.09 ± 0.05	−0.10 ± 0.03	0 ± 0.05	−0.08 ± 0.04	0.09 ± 0.05	−0.01 ± 0.04	0.12 ± 0.04
P_{aw} (kPa)	0.10 ± 0.01	0.21 ± 0.01	0.21 ± 0.01	0.36 ± 0.02	0.25 ± 0.02	0.58 ± 0.04	0.31 ± 0.03	0.64 ± 0.06
EEP (kPa)	0	0	0.04 ± 0.01	0.11 ± 0.02	0.08 ± 0.02	0.27 ± 0.04	0.16 ± 0.03	0.39 ± 0.06
MV (litre min^{-1})	8.40 ± 0.57	18.48 ± 2.16	13.51 ± 0.83	25.43 ± 0.47	16.85 ± 0.49	25.53 ± 0.18	20.41 ± 0.10	29.88 ± 0.85
V_T (ml)	35 ± 2.4	77 ± 9.0	56 ± 3.5	106 ± 2.0	70 ± 2.0	106 ± 0.8	85 ± 0.4	124 ± 3.5

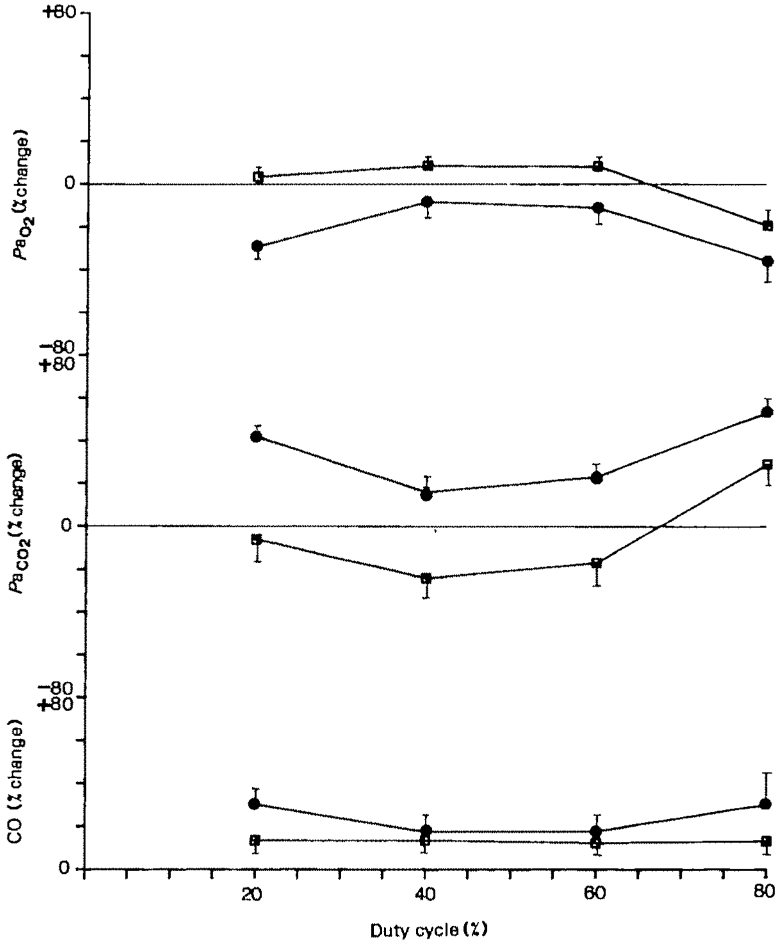

FIG. 3. Arterial blood-gas tensions and cardiac output (CO) related to duty cycle (inspiration time percentage) during HFJV at 4 Hz and $FI_{O_2} = 0.3$ for valve setting 2 (●) and 8 (□) expressed as percentage change from baseline IPPV values.

The 1-min measurements showed an increase in cardiac output of 9%. At valve setting 8, the increase in cardiac output was equal for all measured duty cycles. At valve setting 2, there was a larger increase for 20 and 80% duty cycles.

The results of series 3 ($n = 7$) are presented in table III and figure 4. During the whole experimental period of about 6 h, baseline IPPV values for Pa_{O_2}, Pa_{CO_2} and cardiac output were, respectively: 21.0 ± 0.39 kPa, 4.95 ± 0.04 kPa and 2.98 ± 0.43 litre min^{-1}, with a ventilation minute volume of 3.53 ± 0.27 litre min^{-1}.

Figure 4 shows decreasing gas exchange with increasing frequency. Mean P_{oe} and mean P_{aw} remained constant (table III) while a slight increase in end-expiratory pressure occurred at frequencies greater than 2 Hz. With increasing frequencies, tidal volumes became progressively smaller. Cardiac output was significantly increased for all HFJV settings except for 4 Hz and valve setting 8. Cardiac output was increased, even for frequencies of 1 and 2 Hz and valve setting 8 at which a large decrease in Pa_{CO_2} was measured. The 1-min measurements of cardiac output showed an increase of 7.5%. At frequencies of 8 and 16 Hz, cardiac output was increased further after the 10-min period. At valve setting 8, there was a large increase in cardiac output for 1 and 2 Hz. At 16 Hz, the cardiovascular variables deteriorated progressively and blood-gas samples had to be taken after 5 min in some cases.

TABLE III. *Results of series 3 (mean ± SEM). Valve settings (VS) 2 and 8 for each of five frequencies* (f). P_{oe} = *Oesophageal pressure*; P_{aw} = *airway pressure*; *EEP = end-expiratory pressure*; *MV = ventilation minute volume*; V*T* = *tidal volume*

	f = 1 Hz		*f* = 2 Hz		*f* = 4 Hz	
	VS 2	VS 8	VS 2	VS 8	VS 2	VS 8
P_{oe} (kPa)	−0.14±0.05	−0.02±0.08	−0.13±0.03	−0.05±0.06	−0.13±0.03	0±0.04
P_{aw} (kPa)	0.28±0.02	0.53±0.04	0.24±0.02	0.48±0.03	0.24±0.01	0.36±0.02
EEP (kPa)	0	0	0	0	0.04±0.01	0.11±0.02
MV (litre min^{-1})	13.02±0.19	22.05±0.60	13.97±0.27	24.42±0.68	14.25±0.45	26.05±0.98
*V*T (ml)	217±3.1	368±10.1	116±2.3	203±5.7	59±1.9	109±4.1

	f = 8 Hz		*f* = 16 Hz	
	VS 2	VS 8	VS 2	VS 8
P_{oe} (kPa)	−0.15±0.02	−0.05±0.03	−0.12±0.03	−0.01±0.04
P_{aw} (kPa)	0.16±0.02	0.39±0.01	0.20±0.01	0.46±0.02
EEP (kPa)	0.06±0.01	0.20±0.01	0.10±0.01	0.29±0.03
MV (litre min^{-1})	14.48±0.68	27.62±1.22	13.15±0.32	25.60±1.12
*V*T (ml)	30±1.4	58±2.5	14±0.3	27±1.2

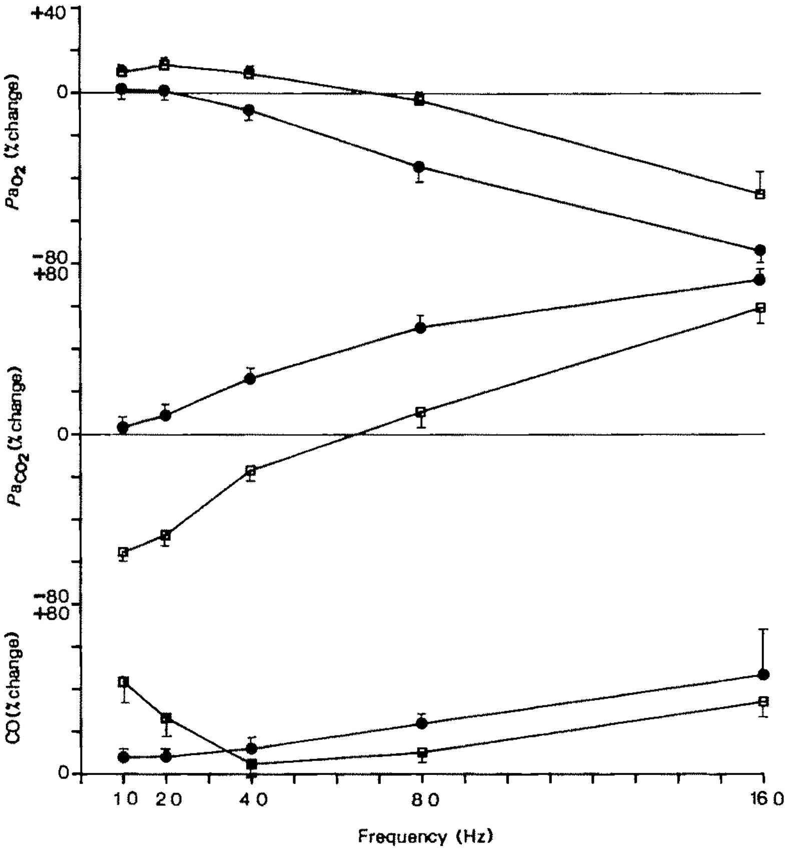

FIG. 4. Arterial blood-gas tensions and cardiac output (CO) related to frequency during HFJV at 40% duty cycle and FI_{O_2} = 0.3 for valve setting 2 (●) and 8 (□) expressed as percentage change from baseline IPPV values.

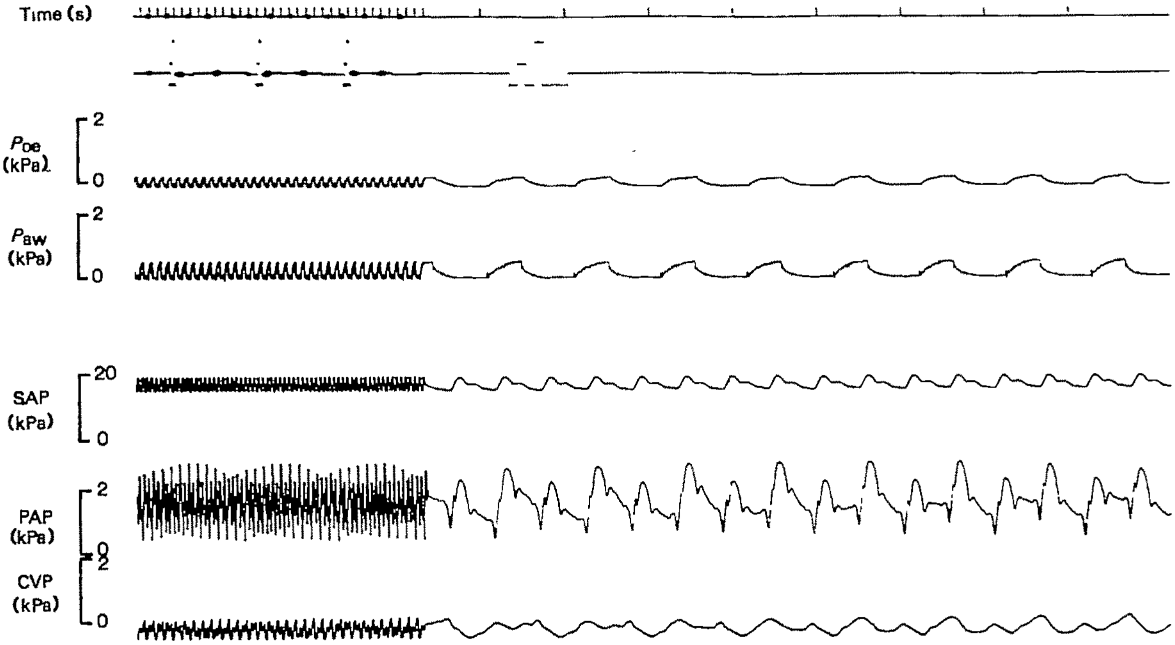

FIG. 5. Oesophageal, airway, systemic arterial, pulmonary artery and central venous pressures during HFJV at 1 Hz, 40% duty cycle and $F_{I_{O_2}} = 0.3$. Pulmonary artery pressure is maximal when peak oesophageal pressure and peak airway pressure coincide with systole.

At frequencies 1–4 Hz, a ventilation-related phasic variation in pulmonary artery pressure was observed. A typical wave pattern with 1 Hz is shown in figure 5, which represents oesophageal, airway, systemic arterial, pulmonary artery and central venous pressures. The tracing of the phasic fluctuations in the PAP shows a typical beat frequency envelope as the difference of two sine waves. Maximum pulmonary artery pressure occurred when peak airway and peak oesophageal pressure coincided with systole. Maxima and minima in PAP occur periodically because of small variations in the phase of interference of the two waves. The systolic and diastolic SAP did not change. HFJV at frequencies 8 and 16 Hz caused only very small phasic variations in PAP.

For the experiments of series 4, three paired combinations of valve setting and duty cycle were chosen from the plot of figure 2, each pair having the same minute volume: 16 litre min^{-1} for 40% duty cycle, valve setting 4 and 30% duty cycle, valve setting 8; 20 litre min^{-1} for 50% duty cycle, valve setting 5 and 90% duty cycle, valve setting 1; 24 litre min^{-1} for 80% duty cycle, valve setting 3 and 60% duty cycle, valve setting 6.

Figure 6 and table IV summarize the results of series 4 ($n = 7$). During the whole experimental time of about 7 h, baseline IPPV values for Pa_{O_2}, Pa_{CO_2} and cardiac output were, respectively: 20.8 ± 0.21 kPa, 4.97 ± 0.05 kPa and 3.36 ± 0.16 litre min^{-1}, with a ventilation minute volume of 3.73 ± 0.18 litre min^{-1}. Although the ventilator minute volume was equal for each pair of HFJV settings without entrainment, blood-gas values were significantly different, except for the Pa_{O_2} of the first pair.

Allowing air entrainment resulted in more pronounced differences of the blood-gas values, with statistical significance for all settings. The differences in blood-gas values within each pair of settings paralleled the differences in duty cycle.

Table IV shows the values for tidal volume with and without entrainment. The quantity of entrainment differed with the HFJV ventilator settings. For 90% duty cycle and valve setting 1 there existed no entrainment at all. Mean P_{oe}, mean P_{aw} and end-expiratory pressure were equal within each pair of settings.

Cardiac output was significantly increased at all isovolumetric settings, even in those where a

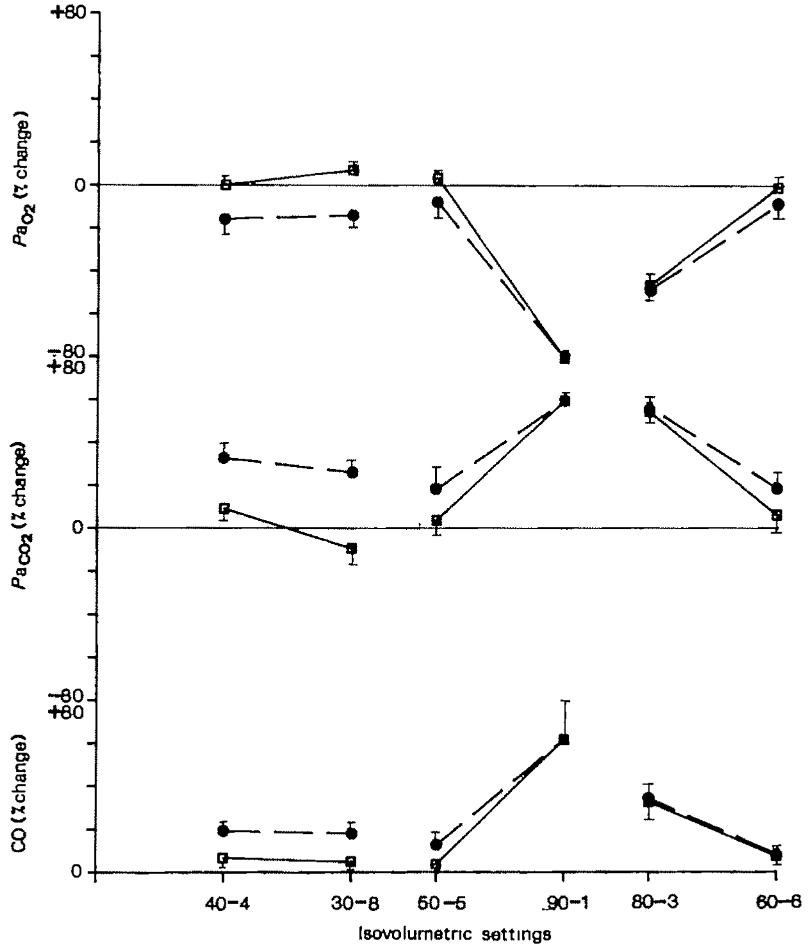

FIG. 6. Arterial blood-gas tensions and cardiac output (CO) of three pairs of isovolumetric combinations of duty cycle and valve setting during HFJV at 4 Hz and $F\text{I}_{O_2} = 0.3$, expressed as percentage change from baseline IPPV values. The solid lines connect the values with entrainment, the dashed lines connect the values without entrainment (see text).

TABLE IV. *Results of series 4 (mean ± SEM). Pairs of valve settings (VS) and duty cycles (DC).* P_{oe} = *Oesophageal pressure;* P_{aw} = *airway pressure; EEP = end-expiratory pressure; MVe = ventilation minute volume with entrainment; MV = ventilation minute volume without entrainment;* V_{Te} = *tidal volume with entrainment;* V_T = *tidal volume without entrainment*

	DC 40 %	DC 30 %	DC 50 %	DC 90 %	DC 80 %	DC 60 %
	VS 4	VS 8	VS 5	VS 1	VS 3	VS 6
P_{oe} (kPa)	−0.03 ± 0.06	0 ± 0.05	−0.01 ± 0.04	−0.04 ± 0.04	0.10 ± 0.03	0.07 ± 0.05
P_{aw} (kPa)	0.26 ± 0.02	0.26 ± 0.02	0.34 ± 0.04	0.28 ± 0.02	0.37 ± 0.02	0.45 ± 0.03
EEP (kPa)	0.03 ± 0.01	0.03 ± 0.02	0.11 ± 0.02	0.16 ± 0.02	0.19 ± 0.02	0.20 ± 0.02
MVe (litre min^{-1})	19.69 ± 0.53	24.08 ± 0.63	23.03 ± 0.57	20.18 ± 0.49	25.80 ± 0.57	24.29 ± 0.42
V_{Te}(ml)	82 ± 2.2	100 ± 2.6	96 ± 2.4	84 ± 2.0	108 ± 2.4	101 ± 1.8
MV (litre min^{-1})	15.87 ± 0.37	16.05 ± 0.43	20.18 ± 0.51	20.22 ± 0.50	24.00 ± 0.63	23.98 ± 0.47
V_T (ml)	66 ± 1.5	67 ± 1.7	84 ± 2.1	84 ± 2.1	100 ± 2.6	100 ± 2.0

positive end-expiratory pressure was present. Within a particular pair of settings, changes in cardiac output paralleled the duty cycle.

DISCUSSION

To investigate the ventilatory minute volume required for HFJV, comparison has to be made between HFJV settings resulting in normal blood-gas partial pressures and minute volume during periods of IPPV. In figure 3, the blood-gas values of ventilator setting 4 Hz, 20% duty cycle and valve setting 8 are almost equal to the baseline IPPV blood-gas values of this series, but the minute volume during HFJV is six times the minute volume during IPPV.

In figure 4, the blood-gas values of ventilator setting 1 and 2 Hz, 40% duty cycle and valve setting 2 are almost equal to the baseline IPPV values of this series, but the minute volume during HFJV is four times the minute volume during IPPV.

Carlon and colleagues (1983) showed that minute volume during HFJV had to be three times as high as during IPPV to obtain comparable blood-gas values. The Pa_{CO_2} measured in their control animals on HFJV was lowest when they used a minute volume of 1200 ml kg^{-1}, and comparable to the Pa_{CO_2} during IPPV when a minute volume of 400 ml kg^{-1} was used.

The ventilatory circuitry and frequency may have influenced the difference in results. As our minute volume reading from the plot of figure 2 does not include entrainment, the comparable blood-gas tensions during HFJV are obtained by even higher minute volumes. Ventilator minute volume for this particular high frequency jet ventilator is regulated through duty cycle and valve setting. The large minute volumes which increased with duty cycle and valve setting are apparent from figure 2. The non-linearity in volume increase is probably caused by the decreasing driving pressure because of the capacitor used.

The results of series 2 (fig. 3) show that, although ventilator minute volume increased with a higher duty cycle, gas exchange was adversely influenced. In our study, a duty cycle of 40% was optimal, which emphasizes the fact that inspiration time percentage is as relevant in HFJV as it is in IPPV. The adverse effect of a duty cycle > 50% on gas exchange is also indicated by the results of series 4. These data complement the results of Calkins and colleagues (1982) who stated that I:E ratios should be greater than 0.25 in dogs. They speculated that gas exchange might be ineffective in humans at high I:E ratios because of the greater expiratory resistance in humans. Attention should be paid to the difference between I:E ratio and duty cycle (see Methods). The diversity in duty cycle setting in patient studies is considerable, so that comparisons with our data are hardly possible. In a recent review (Froese, 1984), the duty cycle setting in HFJV was very briefly considered as a possible important variable with respect to gas trapping. According to Rouby and co-workers (1985), I:E ratio does not play a significant role in carbon dioxide elimination. They found an I:E ratio of 0.43 to be optimal, corresponding to a duty cycle of 30%. Their equipment though, was different, since they used a swivel adaptor with jet nozzle at the proximal end of the tracheal tube. Our data also differ from those presented by Banner, Gallagher and Caruthers-Banner (1983), who concluded that the optimum duty cycle in HFJV for dogs was 20%. They used several criteria to determine the optimal duty cycle, but used a ventilation circuit comparable to that of Rouby's group.

The results of series 3 clearly show that increases in frequency which do not influence ventilator minute volume, have an adverse effect on gas exchange. At frequencies greater than 4 Hz, air entrainment was minimal or even non-existing, thus excluding an influence on inspired oxygen concentration. In this series, the duty cycle setting was fixed at the optimal setting found in series 2.

The results of series 3 (fig. 4) resemble the results presented by Vourc'h and co-workers (1983). Although their studies in patients were undertaken using a different procedure and using an MK800 Acutronics high frequency jet ventilator and rigid bronchoscopes, their results for Pa_{O_2} and Pa_{CO_2} show the same trends as our data from dogs. This indicates that gas exchange mechanisms in HFJV probably are essentially different from those in high frequency oscillation, where even very high frequencies provide adequate ventilation. Despite the theoretical claims proposed during early publications on high frequency ventilation, more recently, Groeger and colleagues (1984) drew attention to the role of convective flow in HFJV.

Rouby and his co-workers (1985) provided evidence, by measuring tidal volumes, that bulk flow during HFJV is the main mechanism of carbon dioxide elimination. Our data, showing a better carbon dioxide elimination in the lower frequencies corresponding with higher tidal volumes (table III), are in agreement with these suggestions.

The experiments of series 4 were performed to examine the influence of ventilation pattern on gas exchange for a fixed ventilator minute volume. Each pair of chosen settings was isovolumetric without air entrainment. The magnitude of air entrainment (tracheal tube open to ambient air) was dependent on the chosen combination of valve setting and duty cycle. Air entrainment was thus variable and depended on the pattern of HFJV. Its effect was difficult to predict in a given situation. The results of series 4 also show that, despite equal minute volumes (preventing air entrainment), gas exchange is highly dependent on the HFJV pattern used, especially the inspiration time percentage. In all our experiments with dogs, cardiac output was increased during HFJV despite a positive end-expiratory pressure in some of the experimental situations (Rankin et al., 1982). This increase in cardiac output could be partly induced by hypercapnia (Morgan et al., 1967; Foëx, 1980), but even in those settings resulting in hypocapnia, a significant increase in cardiac output indicated that, apart from a possible carbon dioxide effect, a direct mechanical effect from the HFJV on the pulmonary circulation may play a role, leading consequently to a reactive enhancement of the cardiac output. At valve setting 8 and frequencies 1 and 2 Hz, there was considerable increase in cardiac output, despite a concomitant decrease in Pa_{CO_2} (fig. 4). Following this HFJV period, a temporary increase in SAP was observed during IPPV. A possible explanation might be a decrease in cerebral perfusion caused by cerebral vasoconstriction as a result of a decrease in Pa_{CO_2} (Reivich, 1964). This impairment of cerebral perfusion then could lead to a reflex increase in cardiac output.

Our study with healthy anaesthetized dogs using the type of HFJV ventilator described in combination with tracheal jet tube, leads to the following conclusions:

(a) During HFJV in the frequency range 1–4 Hz, at least four times the minute volume used during IPPV is needed to guarantee adequate gas exchange in the healthy anaesthetized dog. An even higher minute volume is required with higher frequencies.

(b) Gas exchange during HFJV is optimum when the inspiration time percentage is about 40%.

(c) Increasing frequency in HFJV has an adverse effect on gas exchange in the healthy dog.

(d) The extent of air entrainment depends on the chosen pattern of HFJV.

(e) HFJV does not have a depressant effect on cardiac output compared with IPPV.

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ALFENTANIL FOR CAESAREAN SECTION COMPLICATED BY SEVERE AORTIC STENOSIS

A Case Report

N. REDFERN, S. BOWER, R. E. BULLOCK AND C. J. HULL

SUMMARY

Alfentanil 35 μg kg^{-1}, was used successfully in a patient with severe aortic stenosis, in order to minimize the haemodynamic responses to intubation and surgery during Caesarean section. The baby was delivered apnoeic, unresponsive and with poor muscle tone, but responded rapidly to naloxone. Plasma alfentanil concentrations and percentage binding to plasma proteins were measured in both maternal and neonatal blood. Free drug concentrations were similar in both mother and neonate, but maternal plasma proteins had a higher affinity for alfentanil. Only 67.26% of neonatal plasma alfentanil was bound to plasma protein. This value did not differ significantly from those estimated from the blood of a further 12 healthy neonates.

We report the use of alfentanil in a patient with severe aortic stenosis undergoing Caesarean section. This procedure provided a unique opportunity to compare simultaneous drug concentrations and plasma protein binding in mother and neonate.

Although pregnancy may be well tolerated in patients with severe aortic stenosis (Szekely and Snaith, 1974), anaesthesia for Caesarean section in such circumstances can be hazardous, whether regional or general anaesthetic techniques are used (Arias and Pineda, 1978). Hypotension, such as may accompany extradural or intrathecal anaesthesia, may critically diminish coronary perfusion and lead to cardiac failure. Conversely, hypertension and tachycardia, resulting from intubation of the trachea, may severely compromise left ventricular function.

In patients undergoing anaesthesia for cardiac surgery, high-dose opioid anaesthesia has been used to obtund the responses to intubation and surgery and, thereby, preserve haemodynamic stability (de Lange, Stanley and Boscoe, 1981; Sebel, Bovill and van der Haven, 1982; Bovill et al., 1984). Although it would seem that the use of this technique in Caesarean section represents a conflict of interests between mother and baby, it may be argued that an opioid with a very rapid onset and short duration of action might provide adequate haemodynamic protection to the mother, but cause only transient depression in the neonate.

Alfentanil has been shown to obtund the hypertensive response to tracheal intubation after only 30 s (Black, Kay and Healy, 1984) and, therefore, has a sufficiently rapid onset of action to be effective in a rapid intubation sequence. Since this agent also has a shorter duration of action than any other clinically available opioid, the depressant effects on the neonate might be expected to persist for an acceptably short period.

CASE REPORT

An 18-year-old patient known to have aortic stenosis presented for antenatal care with a 23-week concealed pregnancy. During the second trimester she began to complain of dizzy spells and breathlessness induced by walking up slight inclines or against the wind. The fetus appeared to be normal: there was no evidence of intrauterine growth retardation and antenatal cardiotocography did not reveal any evidence of fetal hypoxia.

By the 34th week of pregnancy the patient was incapacitated by dizziness associated with systolic hypotension (50 mm Hg), and suffered several

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N. REDFERN, B.SC., M.B. B.S., F.F.A.R.C.S.; S. BOWER, M.B. B.S., PH.D.; R. E. BULLOCK, M.A., M.R.C.P., F.F.A.R.C.S.; C. J. HULL, M.B. B.S., F.F.A.R.C.S.; Department of Anaesthesia, University of Newcastle upon Tyne, Newcastle. Accepted for Publication: April 3, 1987.

Correspondence to N.R.

TABLE I. *Clinical observations of the neonate, using the Apgar scoring system*

	1 min	2 min	10 min
Heart rate	1	2	2
Ventilatory effort	0	0	2
Tone	0	0	2
Irritability	0	0	2
Colour	1	2	2
Score	2	4	10

"fainting" attacks. A Doppler ultrasound study estimated the systolic gradient across the aortic valve to be approximately 70 mm Hg. It was decided to proceed to Caesarean section under general anaesthesia using an opioid to obtund the responses to intubation and surgery.

Anaesthesia was induced using etomidate 12 mg and alfentanil 1.75 mg (35 μg kg^{-1}). Muscle paralysis was achieved with suxamethonium in the first instance, followed by pancuronium 5 mg. The lungs were ventilated artificially and anaesthesia maintained with 67% nitrous oxide in oxygen and 0.5% halothane.

Twelve minutes after the induction of anaesthesia (2 min after uterine incision) an apnoeic infant weighing 2040 g was delivered. The placenta was normal, and the liquor was not meconium stained. Muscle tone was poor and the baby did not respond to stimuli. One minute after delivery a tracheal tube was inserted and artificial ventilation instituted. The Apgar score was 2 (table I). After 1 min of controlled ventilation the baby was observed to be pink, with a heart rate of 140 beat min^{-1}, but remained apnoeic, atonic and unresponsive (Apgar score 4).

Eight minutes after delivery, naloxone 100 μg (50 μg kg^{-1}) was given. Almost immediately the infant became alert and commenced spontaneous breathing (Apgar score 10). However, artificial ventilation was continued electively for 3 days because of mild respiratory distress syndrome. The baby's further progress was straightforward, and she has developed normally.

The anaesthetic technique was successful in preventing a response to intubation; maternal arterial pressure remained at its preoperative value (90/60 mm Hg) throughout induction. After induction, arterial pressure decreased briefly to 70/50 mm Hg, but returned to the preoperative value before the abdominal incision was made. During the 5-min period between incision and delivery the arterial pressure remained unchanged. After delivery the systolic arterial pressure remained within the range 90–100 mm Hg.

Five months after the birth of her baby, and when symptom free, the mother underwent cardiac catheterization. An aortic valve systolic gradient of 100 mm Hg, and a peak left ventricular pressure of 195 mm Hg, were recorded. The aortogram showed a thickened, immobile, deformed valve and some supravalvular narrowing. There was grade 2/4 aortic regurgitation and good left ventricular function. The ECG was normal.

Blood sampling

At delivery of the infant, maternal and cord blood samples were taken for synchronous estimations of alfentanil concentrations and plasma protein binding. A further specimen of blood was taken from the baby 48 min after delivery.

Plasma concentrations were estimated by radioimmunoassay (Bower and Hull, 1982). Plasma protein binding of alfentanil was estimated in both neonatal and maternal blood using an equilibrium dialysis technique (Bower, 1981) (table II).

Protein binding and free drug concentrations

Free drug concentrations were calculated from total plasma concentrations by means of the expression:

$$[\text{FREE}] = [\text{TOTAL}] \times (1 - \text{bound fraction})$$

It was found that, although the maternal total concentration was approximately three times that in the neonate, free concentrations were very similar (table II).

Protein binding of alfentanil in neonates

Since the above difference in maternal and neonatal binding ratios could conceivably have been the result of some individual abnormality in

TABLE II. *Alfentanil concentrations and percentage binding to plasma proteins in mother and infant*

	Mother	Infant
Plasma alfentanil concn at delivery (ng ml^{-1})	67	22.4 (cord blood)
Drug bound in plasma (%)	88	67
Free drug concn in plasma (ng ml^{-1})	8.04	7.4
Total alfentanil concn in plasma 48 min after delivery (1 h after alfentanil) (ng ml^{-1})		12.5

TABLE III. *Percentage binding of alfentanil to plasma proteins in cord blood taken from 13 neonates. *Mean of four estimations. All other values are the means of duplicate estimations. †Infant described in the present case report*

	Binding (%)	Delivery at
	67.26*†	34 Weeks
	76.95	Full term
	56.93*	35 Weeks
	77.8	Full term
	77.02	Full term
	78.47	Full term
	75.62	Full term
	71.18	Full term
	71.19	Full term
	70.57	Full term
	75.87	Full term
	71.61	Full term
	74.14	Full term
Mean	72.66	
SD	5.81	
SEM	1.61	

the neonate concerned, alfentanil binding was investigated *in vitro* in cord blood taken from a further 12 healthy neonates. The results are shown in table III. It can be seen that the value of 67.26% in the studied neonate did not differ significantly from the sample mean of 72.66%.

DISCUSSION

It might be expected that the disposition of drug across a permeable membrane separated by two different protein solutions would be characterized by the simple model:

$$\begin{tikzcd}
{[B1]} \arrow[d, shift left, harpoon] & {[B2]} \arrow[d, shift left, harpoon] \\
{[F1]} \arrow[u, shift left, harpoon] \arrow[r, shift left, harpoon] & {[F2]} \arrow[u, shift left, harpoon] \arrow[l, shift left, harpoon]
\end{tikzcd}$$

where $B1$, $B2$ and $F1$, $F2$ are the concentrations of bound and free drug in protein solutions 1 and 2, respectively. At equilibrium, the free drug concentrations are equal, that is $[F1] = [F2]$. Free drug on each side of the membrane is also in equilibrium with bound drug in a ratio governed by the corresponding association constant. Thus when the two proteins have differing concentrations or association constants, or both, the bound concentrations will differ also. Since the total drug concentration is the sum of bound and free fractions, this value may be different in the two solutions.

If the placenta were freely permeable to alfentanil, with rapid equilibration, then the free concentrations in mother and infant would be expected to be equal. Taking the observed maternal concentration of 67 ng ml^{-1}, of which 12% was unbound, the free concentration can be calculated to be 8.04 ng ml^{-1}. Similarly, of the simultaneously measured neonatal concentration (22.4 ng mg^{-1}) 23% was unbound, yielding a free concentration of 7.4 ng ml^{-1}. The close similarity between maternal and neonatal free concentrations supports the hypothesis that alfentanil equilibrates freely and rapidly across the placenta.

The mean percentage binding of 72.66% (SEM 1.61) in neonatal blood (table III) may be compared with the value of 88.65% (SEM 0.45) found in the blood of 42 healthy adult subjects (Bower and Hull, 1982). In both groups, protein binding was estimated using the same technique, in the same laboratory, by the same investigator. The mean values differed significantly ($P < 0.001$).

These results differ from the data obtained by Meistelman and his colleagues (Meistelman et al., 1985), who estimated the bound percentage of alfentanil in the blood of nine infants to be 62.9%. Since they also estimated maternal protein binding to be only 82.5%, but with a similar coefficient of variation, the differences from our data are likely to be attributable to methodological factors.

In the same study, Meistelman's group also showed that the neonatal concentrations of alpha$_1$-acid-glycoprotein (AGP) are only some 44% of adult values. It has been suggested (Meuldermans, Hurkmans and Heykants, 1982) that AGP is responsible for at least part of the protein binding characteristics of alfentanil. Therefore, it is possible, as proposed by Meistelman, that lower protein binding in neonates is the result of this difference in AGP concentration.

It was disturbing to note that the infant in our case was not only apnoeic with bradycardia and dusky extremities, but also "floppy" with no evidence of reflex irritability. Neonatal hypotonia may be caused by hypoxia, hypotension or anaesthesia. Since the antepartum cardiotocograms were normal, the placenta was grossly normal and the liquor was not meconium stained, it is unlikely that the fetus was hypoxic when delivered. Maternal hypotension is unlikely to have been the cause of fetal hypoxia, since the decrease in arterial pressure following induction was very brief, with recovery to the preoperative value at least 5 min before delivery. After controlled ventilation for 1 min the infant became pink with a normal heart rate, but remained floppy and unresponsive. Following a single dose of naloxone the baby became active, moved its limbs and attempted to cry. It is likely that the initially poor Apgar scores were the result of the narcotic effects of alfentanil.

At delivery, maternal and neonatal free drug concentrations were very similar (table II). Therefore, the pharmacological effects might also be expected to be similar. Since the mother was anaesthetized, it is not possible to make direct comparison. However, the observed maternal alfentanil concentration (67 ng ml^{-1}) can be considered in the context of other detailed studies on the respiratory effects of alfentanil. The data obtained by O'Connor, Escarpa and Prys-Roberts (1983) suggest that a plasma concentration of 67 ng ml^{-1} would be expected to decrease the gradient of a carbon dioxide response curve, but have no significant effect on ventilatory minute volume, frequency or PA_{CO_2}. This contrasts with the apnoeic, hypotonic infant in our report. It appears that the neonate was much more susceptible to alfentanil than the mother.

It should be noted that after 1 h the neonatal plasma concentration had decreased to 12.5 ng ml^{-1}. This modest change from the value measured at delivery is consistent with the 12-min delay between i.v. administration and delivery, during which extensive distribution would have occurred in both mother and baby. Indeed, the observed rate of decline probably indicates the rate of drug elimination.

CONCLUSIONS

The data lead to the following conclusions:

(1) The placenta presents no greater barrier to alfentanil transfer than a simple dialysis membrane.

(2) The lower concentrations of alfentanil in neonatal plasma are not the result of slow placental transfer or rapid distribution in the fetus, but of the differing affinities of plasma proteins in maternal and neonatal blood.

(3) Equilibration of free drug across the placenta is rapid, so that the free neonatal concentration may be expected to follow the maternal concentration closely until delivery.

(4) It should not be assumed that plasma concentrations in the neonate will decline after delivery as if the drug had just been given i.v., with the expectation that the effect will persist for a few minutes only.

(5) While the use of moderate doses of alfentanil during anaesthesia for Caesarean section may be of benefit to the haemodynamically compromised mother, the baby should be expected to be severely depressed. Therefore, this technique would appear unsafe unless there are adequate facilities for the management of an apnoeic, anaesthetized infant.

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MANAGEMENT OF TRACHEOMALACIA IN ASSOCIATION WITH CONGENITAL TRACHEO–OESOPHAGEAL FISTULA

P. T. CONROY AND N. R. BENNETT

SUMMARY

Tracheomalacia is commonly associated with oesophageal atresia and tracheo–oesophageal fistula. Severe cases may present with life threatening cyanotic and apnoeic attacks following surgical repair of the oesophageal atresia. The anaesthetic, and surgical management (by tracheopexy), of such a case are described.

Tracheomalacia occurs commonly in association with oesophageal atresia and tracheo–oesophageal fistula (Wailloo and Emery, 1979). Tracheomalacia is a term which describes weakness of the tracheal wall which may cause sufficient narrowing of the lumen to produce ventilatory symptoms. Recurrent chest infections and apnoeic or cyanotic spells leading to cardiac arrest may occur after oesophageal repair. The purpose of this case report is to stress the importance of the association between tracheomalacia and congenital oesophageal atresia—an association which is not well documented in the anaesthetic literature—and to outline the anaesthetic management of severe cases which require surgical treatment by tracheopexy.

CASE REPORT

A 3-kg female infant was delivered vaginally at term. It was noted that a feeding tube failed to pass down the oesophagus and a presumptive diagnosis of oesophageal atresia was made. No other anomalies were present; there were no ventilatory problems, stridor was absent, and the cry was normal. A double lumen Replögle tube was passed into the upper pouch to provide some protection from aspiration, and the infant was transferred to the Sheffield Neonatal Surgical Unit. Subsequently, a right thoracotomy was performed. Through an extrapleural approach, a low tracheo–oesophageal fistula was ligated and the two ends of the oesophagus were anastomosed with a trans-anastomotic feeding tube in place.

Immediately before surgery, atropine 0.06 mg was given i.v. and awake intubation of the trachea was performed with a 3.0-mm uncuffed Magill tube. Anaesthesia was maintained with nitrous oxide in oxygen through a Jackson–Rees modification of Ayre's T-piece at a flow of 3 litre min^{-1}. When it had been ensured that there was no significant leak into the stomach during positive pressure ventilation, atracurium 1 mg was administered i.v.; manual ventilation of the lungs was performed for the duration of the operation with increments of atracurium, given as required. There were no significant anaesthetic or surgical problems and on completion of surgery, the infant resumed adequate spontaneous ventilation without the need for antagonism of residual neuromuscular blockade. Extubation was performed without incident.

The infant remained well until the 4th day after operation, when there was an acute episode of cyanosis. A chest x-ray revealed a left sided pneumothorax and her condition improved following the administration of oxygen, nasopharyngeal suction and insertion of a chest drain. During the following days there were further acute episodes of cyanosis which were often associated with feeding and were preceded by clinical evidence of upper airway obstruction. One episode was associated with severe bradycardia which required external cardiac compression and oxygen by positive pressure ventilation. Between

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P. T. CONROY, M.B. CH.B., F.F.A.R.C.S.; N. R. BENNETT, M.B. CH.B., F.F.A.R.C.S.; Department of Anaesthetics, Sheffield Children's Hospital, Sheffield, Yorks. Accepted for Publication: October 2, 1986.

episodes the infant appeared normal. Barium studies revealed no evidence of narrowing at the anastomotic site which could lead to pulmonary aspiration, and there was no evidence that the fistula had recurred.

A systolic murmur had been heard at the left sternal edge. Chest x-ray and cardiac ultrasound revealed no abnormalities, and a cardiac lesion was considered unlikely after cardiological consultation. However, a lateral chest x-ray revealed narrowing of the upper portion of the trachea with evidence of compression during barium swallow. A diagnosis of tracheomalacia was suggested.

Provisional arrangements were made to perform tracheopexy and the infant was transferred to theatre after premedication with atropine 0.1 mg i.m. After the application of a precordial stethoscope, ECG electrodes and arterial pressure cuff, the insertion of a rectal thermometer probe and cannulation of a peripheral vein, anaesthesia was induced with nitrous oxide and halothane in oxygen. Bronchoscopy was performed using a Storz bronchoscope (internal diameter 2.5 mm) while anaesthesia was maintained by attaching an Ayre's T-piece system to the side arm of the bronchoscope and insufflating oxygen and halothane. The findings were that there was intermittent collapse at the lower end of the trachea and the diagnosis of tracheomalacia was confirmed.

After removal of the bronchoscope, the trachea was intubated with an uncuffed, 3.0-mm reinforced silicon oral tube (Cory Brothers Ltd). Anaesthesia was maintained with nitrous oxide in oxygen delivered through a Jackson–Rees modification of Ayre's T-piece as above. Again, manual ventilation of the lungs was performed for the duration of surgery with increments of atracurium, as necessary.

Tracheopexy was performed through a cervical approach. Through a low transverse cervical incision the strap muscles were divided and the manubrium split. The edges of the manubrium were retracted laterally and the isthmus of the thymus divided. The trachea was then revealed passing caudally and posteriorly deep to the innominate vein and right innominate artery (fig. 1). Three silk sutures were placed through the trachea into the posterior edge of the manubrium and tied sufficiently tightly to support its anterior wall. Additional supporting sutures were placed into the adventitia of the aortic arch and innominate artery. Thus the anterior wall of the trachea was drawn forwards towards the sternum. On completion of surgery the infant resumed spontaneous ventilation and extubation was performed. She was then returned to the surgical unit where she made an uneventful recovery and had no further cyanotic episodes.

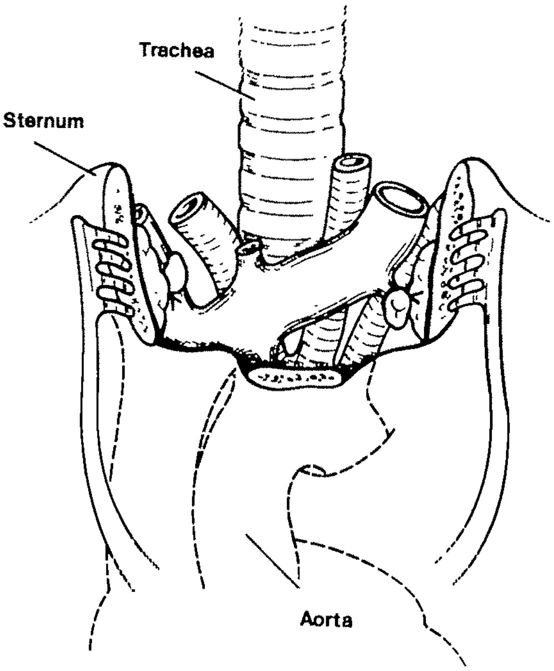

FIG. 1. Cervical approach for tracheopexy.

DISCUSSION

Tracheomalacia can be defined as a condition in which there is weakness of the tracheal wall as a result of softening of the supporting cartilage and hypotonia of the myoelastic elements (Baxter and Dunbar, 1963). Tracheomalacia may be divided into two types: primary and secondary.

In primary tracheomalacia the condition is congenital. It may be an isolated finding or be associated with other congenital anomalies—cleft palate, choanal atresia and oesophageal atresia. In secondary tracheomalacia the condition is acquired. The common origin of the trachea and oesophagus from the primitive foregut makes it likely that in individuals in whom the oesophagus is developmentally abnormal, tracheal anomalies will co-exist such as the association between tracheo–oesophageal fistula and oesophageal atresia.

Following surgical correction of tracheo–oesophageal fistula and oesophageal atresia, affected children may have stridor, recurrent cough, wheeziness, dyspnoea and even apnoeic attacks leading to cardiac arrest. Symptoms may be attributed to respiratory tract infection resulting from the inhalation of regurgitated contents, with little attention being paid to the possibility of tracheal anomalies accounting for the symptoms. Early reviews (table I) of surgical and anaesthetic management of oesophageal atresia and tracheo–oesophageal fistula failed to include tracheomalacia as a postoperative problem, although ventilatory complications were usually the commonest cause of morbidity and mortality. Dudley and Phelan (1976), in a follow-up of respiratory complications in long term survivors of oesophageal atresia, concluded that recurrent inhalation of milk and food consequent upon disordered oesophageal motility is the major factor causing respiratory complications. However, Wailloo and Emery (1979) showed an almost invariable association between tracheo–oesophageal fistula and tracheomalacia; 40 children with tracheo–oesophageal fistula were analysed postmortem; only six tracheae were entirely normal: 75% had a reduction in length of cartilage; 60% showed an increase in the length of transverse muscle and 65% had a wider than average internal diameter. The fistula site could not be used as a marker for tracheal defects. The authors concluded that the effect of these changes is an alteration in the shape of the trachea so that the normal horseshoe shape is lost. This tends to make the trachea soft and floppy, potentiating antero-posterior collapse of the walls during coughing, ventilation and feeding where posterior compression of the trachea by food in the oesophagus may occur.

It has been suggested (Davies and Cywes, 1978) that tracheomalacia is associated with tracheo–oesophageal fistula because, at birth, the proximal oesophageal pouch, in contrast to the distal oesophageal remnant, has become dilated and its muscular wall hypertrophied. The proximal pouch exerts a compressive force on the trachea from early in fetal life, affecting the development of the tracheal wall. A second hypothesis, by the same authors, proposes that the presence of a fistula leads to loss of intratracheal pressure in the fetus causing abnormal development of the trachea. In the normal fetus the tracheobronchial tree is distended by fluid, provided there is a competent glottic mechanism. However, this splinting effect will be lost by drainage of fluid through a tracheo–oesophageal fistula. The tracheal wall then becomes more susceptible to the effects of external pressure.

The cause of cyanotic episodes in children following repair of oesophageal atresia and tracheo–oesophageal fistula can be difficult to determine: oesophageal stricture with aspiration, a recurrent or second fistula, gastro–oesophageal reflux, anastomotic leak, cardiac or neurological defect must all be excluded. A lateral chest x-ray

TABLE I. *Reviews of surgical and anaesthetic management of oesophageal atresia and tracheo–oesophageal fistula*

	No. of patients	Commonest cause of postoperative complications	Incidence of respiratory complications	Associated tracheomalacia
Shaw, Paulson and Siebel (1955)	61	Respiratory complications (including two deaths from convulsions and severe cyanotic episodes)	Not reported	Not reported
Haight (1957)	200	Respiratory complications and associated anomalies	Not reported	Not reported
Waterston, Bonham Carter and Aberdeen (1962)	218	Respiratory complications	Approximately 50%	Not reported
Stogsdill, Miller and Stoelting (1967)	136	Respiratory complications	41% when endotracheal intubation used during anaesthesia. 55% when trachea not intubated	Not reported
Calverley and Johnston (1972)	90	Respiratory complications (including 11 fatal cardiac arrests)	48%	Two cases of laryngomalacia

may reveal segmental narrowing of the trachea and screening of the trachea during barium swallow may reveal tracheal compression.

Confirmation of the diagnosis of tracheomalacia is made by bronchoscopy, where segmental tracheal narrowing is usually obvious on direct vision. Bronchoscopy is indicated in all children who develop recurrent apnoeic spells after repair of oesophageal atresia when causes other than tracheomalacia have been excluded. Benjamin, Cohen and Glasson (1976) treated 80 infants with congenital tracheo–oesophageal fistula: 21 developed ventilatory symptoms following ligation of fistula and oesophageal anastomosis; in 20 of these patients tracheomalacia was confirmed at bronchoscopy. All 20 infants had a characteristic brassy cough. The cases were classified as severe, moderate or mild. The seven patients in the severe group had upper respiratory tract obstruction with stridor, and cyanotic and apnoeic attacks which occurred in the first 2 months; four patients had one or more cardiac arrests.

The moderate group included three patients who developed symptoms during the first 2 months of life, while five remained symptom free until the 5th month. They developed stridor and wheezing with frequent respiratory infections, during which cyanotic episodes occurred.

The five mild cases had occasional respiratory infections with croup or bronchitis associated with sputum retention. Symptoms did not occur in this group until about the age of 6 months.

Five of the patients in the severe group were successfully treated by tracheopexy via thoracotomy; the patients in the moderate group required regular physiotherapy with home facilities for pharyngeal aspiration; the patients in the mild group were managed by intermittent chest physiotherapy. Filler, Rosello and Lebowitz (1976) also described three cases of life threatening anoxic spells caused by tracheal compression after repair of oesophageal atresia.

The majority of patients with tracheomalacia associated with oesophageal atresia are asymptomatic or have recurrent minor chest infections which improve with age. However, patients who develop life threatening "death attacks" or require emergency and prolonged hospitalization can be successfully treated by tracheopexy. Tracheopexy is a relatively new surgical procedure. Although the operation can be carried out via thoracotomy, the cervical approach (Vaishnev and Mackinnon, 1986) provides the surgeon with easier and more direct access to the trachea. It allows precise insertion of sutures and, as the lung is not retracted, no impairment of ventilation. Five patients have been successfully treated in our hospital over recent years (table II) by this approach. During the procedure anaesthetic problems include kinking of the tracheal tube, obstruction of the great vessels and haemorrhage. The use of a kink-resistant tube, monitoring of breath sounds by precordial stethoscope and manual ventilation of the lungs are essential to the safe management of these patients, and permit the early detection of airway and ventilatory problems during surgery. Careful surgical placement of sutures in the adventitia of the great vessels ensured that blood loss was usually small: of the five patients only one child required blood transfusion. Difficulty with intubation was encountered in one patient. One child developed

TABLE II. *Five cases of severe tracheomalacia associated with congenital tracheo–oesophageal fistula managed by tracheopexy*

Patient No.	Age at tracheopexy	Symptoms	Intraoperative comments	Postoperative course
1	4 years	Recurrent chest infection. Mouth-to-mouth resuscitation at home	No problems	Uneventful
2	3 months	Cyanotic attacks with feeding. Apnoeic attacks	Difficult intubation	Uneventful
3	3 months	Apnoeic attacks	Required blood transfusion	Uneventful
4	15 months	Apnoeic attacks, cyanotic attacks during feeds	No problems	Required 4 days ventilation because of development of pneumonia
5	2 months	Apnoeic attacks	No problems	Uneventful

pneumonia in the postoperative period and required ventilation for 4 days. In all other patients the trachea was extubated immediately after surgery and the patient nursed in oxygen enriched humidified air. This was an added precaution because of the possible development of airway oedema caused by bronchoscopy before undertaking tracheopexy. In another review, Schwartz and Filler (1980) administered anaesthesia via a ventilating bronchoscope so that relief of tracheal compression could be assessed directly during the course of surgery. However, the advantages of this technique must be outweighed by the trauma to the trachea caused by prolonged instrumentation.

In a recent study, Wiseman, Duncan and Cameron (1985) described the management of tracheomalacia in three neonates using a tracheostomy and long term continuous positive airway pressure (CPAP). Treatment times ranged from 13 to 25 months, each child being eventually weaned from CPAP and decannulated. The authors claim that this method of management is a reasonable alternative to tracheopexy. However, such a prolonged stay in hospital—in addition to the hazards of tracheotomy—would appear to be a major disadvantage when compared with the rapid recovery and lack of postoperative complications in patients managed by tracheopexy.

In conclusion, the diagnosis of tracheomalacia must be considered as a cause of cyanotic and apnoeic attacks in any infant who has undergone surgical repair of oesophageal atresia. Severe cases can be managed successfully by performing tracheopexy. Intraoperative problems are usually few, provided meticulous attention is paid to maintaining patency of the airway and ventilation. The postoperative course is usually uneventful.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

GLASGOW MEETING

JUNE 26–27, 1987

(The name of the author presenting the paper is shown in bold type. * Indicates non-member.)

EFFECT OF OXYGEN ON ARTERIAL SATURATION DURING INDUCTION OF ANAESTHESIA WITH PROPOFOL

K. D. THOMSON* AND J. P. PAYNE
Research Department of Anaesthetics, Royal College of Surgeons of England and St Peter's Hospitals, London

There have been reports of prolonged apnoea and hypotension associated with induction of anaesthesia with propofol. Accordingly, during induction of anaesthesia with propofol 100 patients were studied; 50 patients breathed 100% oxygen and 50 breathed air. The two groups were not significantly different for age and weight. Changes in oxygen saturation, measured with a Biox 3700 pulse oximeter, and the occurrence and duration of apnoea were compared between groups.

Patients were premedicated with temazepam 20 mg by mouth 2 h before surgery. Baseline measurements of Sa_{O_2}, heart rate and arterial pressure (Dinamap 854) were taken. Anaesthesia was induced with propofol 1.5–2.5 mg kg^{-1}. At induction each patient was breathing either air or oxygen through a mask. Tidal volume was monitored with a Wright's respirometer and end-tidal carbon dioxide with a capnograph (Datex). After induction of anaesthesia an airway was inserted and the mask was connected to a Magill's attachment through which anaesthesia was continued with halothane in nitrous oxide and 33% oxygen. Recordings were continued until the patient was transferred to the operating room.

There was a mean decrease in Sa_{O_2} of 10.8% from baseline measurements in the group who breathed air during induction (table I); in the group who breathed oxygen the mean Sa_{O_2} increased above the baseline measurements. The mean duration of apnoea in the oxygen group was 2.3 times longer than in the group who breathed air. Mean reductions in systolic arterial pressure of 23.6% (air group) and 19.2% (oxygen group) and increases in heart rate of 11.9% (air group) and 11.2% (oxygen group) were not significantly different.

TABLE I. *Results (mean ± SEM (range)).*
$^*P < 0.05$; $^{***}P < 0.001$

	50 patients breathing air	50 patients breathing oxygen
Sa_{O_2}		
Baseline	96.4 ± 0.2 (93–100)	95.5 ± 0.2 (92–98)
Minimum	86.0 ± 0.6 (75–96)***	96.4 ± 0.4 (90–99)
Duration of apnoea (s)	33.9 ± 3.6 (0–108)*	77.8 ± 6.4 (0–276)
Apnoea > 20 s	34 (68%)	48 (96%)

COMPARISON OF THE HAEMODYNAMIC RESPONSES TO INDUCTION OF ANAESTHESIA WITH EITHER PROPOFOL OR THIOPENTONE IN ASA III PATIENTS

M. E. BONE*, K. MOBLEY*, D. FELL AND G. SMITH
University Department of Anaesthesia, Leicester Royal Infirmary, Leicester

Hypotension has been reported following induction of anaesthesia with propofol in fit patients (Rolly et al., 1985), but there is little information in ASA III and IV patients. This study has investigated haemodynamic responses to induction of anaesthesia and tracheal intubation in 12 ASA III patients receiving either propofol 1.5–2.0 mg kg^{-1} or thiopentone 4.5–5.0 mg kg^{-1}. Premedication comprised diazepam 5–10 mg by mouth. In the anaesthetic room, continuous ECG and direct arterial pressure were recorded. At induction of anaesthesia, fentanyl 100 µg was given i.v. followed 1 min later by either thiopentone or propofol over 40–60 s, then vecuronium 0.1 mg kg^{-1}. The lungs were ventilated with 33% oxygen in nitrous oxide using a Bain system with a fresh gas flow to achieve normocapnia and the trachea was intubated 2 min after administration of the vecuronium.

The groups did not differ with respect to age, weight, medication and surgery undertaken. All patients had extensive atheromatous disease involving the coronary and cerebral circulations. There was no inter-group difference in baseline haemodynamic measurements. The mean induction dose of propofol was 1.8 ± 0.18 mg kg^{-1} (mean ± SEM) and loss of consciousness was achieved at a mean time of 62.5 ± 3.6 s. The mean induction dose of thiopentone was 4.7 ± 0.37 mg kg^{-1} and loss of consciousness was achieved at a mean time of 72.3 ± 4.7 s.

In the propofol group, significant hypotension occurred after induction in comparison with the baseline values, comprising 37% for systolic, 31% for diastolic and 34% for mean arterial pressure (MAP). These reductions were significantly greater ($P < 0.05$) than those in the thiopentone group.

One minute after tracheal intubation, arterial pressures returned to values similar to those at baseline. At 3 and 5 min following intubation in the thiopentone group, arterial pressure did not differ from the baseline value. However, in the propofol group, systolic arterial pressure was significantly lower ($P < 0.05$) than baseline value.

Heart rate in the propofol group was significantly less than that in the thiopentone group following induction of anaesthesia ($P < 0.05$). Immediately after intubation there was no difference between groups, but at 5 min, heart rate in the propofol group was again lower ($P < 0.05$) than in the thiopentone group.

The data suggest that, in ASA III patients, the recommended reduction in dose of an induction agent should be relatively greater for propofol than for thiopentone.

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CLONIDINE PREMEDICATION POTENTIATES ISOFLURANE-INDUCED HYPOTENSION

T. E. WOODCOCK*, R. K. MILLARD*, J. DIXON* AND C. PRYS-ROBERTS
Sir Humphry Davy Department of Anaesthesia, University of Bristol, Bristol Royal Infirmary

Clonidine is an anthihypertensive agent which reduces sympathetic outflow by central alpha-2-adrenoceptor stimulation. It decreases the MAC of halothane (Kaukinen and Pyykko, 1979) and reduces sodium nitroprusside requirements for induced hypotension (Ghignone et al., 1986). Our study sought to determine whether clonidine premedication could facilitate isoflurane-induced hypotension by reducing the concentration of vapour necessary to achieve hypotension during ear or nose surgery.

Twenty patients were randomly allocated to control or treatment groups. All patients were premedicated with temazepam 0.3 mg kg^{-1} 2 h before operation, and anaesthesia was induced with fentanyl 2.5 µg kg^{-1}, thiopentone 5 mg kg^{-1}, and vecuronium 0.1 mg kg^{-1}. Anaesthesia was maintained with an i.v. infusion of fentanyl 1.5 µg kg^{-1} h^{-1} and 1 % isoflurane in oxygen. End-tidal carbon dioxide was maintained by positive pressure ventilation at 4.5–5 vol %. When hypotension was required it was induced by initiating a self-tuning control program on a BBC microcomputer which adjusted the concentration of isoflurane delivered from a calibrated vaporizer to regulate the mean intra-arterial pressure to 50 mm Hg (Millard et al., 1987). Patients allocated to the treatment group additionally received clonidine 0.6 mg by mouth with their premedication. Patients in whom there was tachycardia (heart rate 100 beat min^{-1} or more) or failure to achieve hypotension 10 min after initiating control received labetalol 5 mg i.v.

Five of 10 patients in the control group required labetalol to induce hypotension satisfactorily (three for tachycardia), compared with one of 10 in the clonidine-treated group (Fisher's exact probability = 0.07; ns). In all patients hypotension was achieved within 15 min of initiating control. Patients who had received clonidine required lower isoflurane concentrations to maintain hypotension at 50 mm Hg, for periods ranging from 21 to 155 min, than the control group ($P < 0.01$, Mann–Whitney U test). The mean isoflurane concentrations were 1.37±0.65% (treated) *v.* 2.25±0.79% (control) ($P < 0.02$). No adverse effects were associated with the use of clonidine. We conclude that oral clonidine premedication reduces vapour requirements for isoflurane-induced hypotension and may reduce the need for supplementary use of a beta-adrenoceptor antagonist.

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PLASMA GLUTATHIONE S-TRANSFERASE CONCENTRATIONS IN MAN AFTER ENFLURANE ANAESTHESIA

L. M. ALDRIDGE*, L. G. ALLAN*, A. J. HUSSEY*, G. J. BECKET* AND G. B. DRUMMOND
Departments of Anaesthetics and Clinical Chemistry, Royal Infirmary, Edinburgh

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LIVER FUNCTION IN CHILDREN UNDERGOING DAILY NITROUS OXIDE AND ISOFLURANE ANAESTHESIA

S. J. POWER, J. G. DIAMOND* AND **R. M. JONES**
Department of Anaesthetics, United Medical & Dental Schools of Guy's and St Thomas' Hospitals, London

Infants and children with malignancy receiving daily radiotherapy must be completely immobile during the period of irradiation. It is also important that they should recover rapidly, causing as little disruption to their routine as possible. This can be achieved by heavy sedation or general anaesthesia, although Brett, Wara and Hamilton (1986) believe the latter technique to be the method of choice. However, following evidence (Lewis and Blair, 1982; Whitburn and Sumner, 1986) that halothane-induced liver damage probably does occur in children, this inhalation agent may not be the drug of choice. Therefore, in this study we administered daily isoflurane anaesthetics to children receiving radiotherapy and assessed their hepatic function.

After parental informed consent, children scheduled to undergo daily radiotherapy for a period of 10 days or longer, were studied. Each treatment took place at about 08.30 and the children were unpremedicated. Anaesthesia was induced with 3–5% isoflurane in 66% nitrous oxide in oxygen delivered via a Mapleson E system. Isoflurane concentration was then reduced to 1–2% as necessary. Following induction, monitoring was established using an ECG, a pulse oximeter, and a respiration monitor. The procedure was completed in about 20 min and during the treatment period the children and monitors were observed by the use of closed-circuit television. Blood was withdrawn for estimation of liver function tests after induction of anaesthesia on the first day of therapy and at 1-week intervals thereafter. The following were measured: total bilirubin, aspartate amino transferase (AST), gamma glutamyl transpeptidase (gamma GT) and alkaline phosphatase (ALP).

Seven children were studied with a mean age 39 (range 15–59) months. All the children except one with acute lymphoblastic leukaemia had intracerebral malignancy. The mean number of treatments received was 23 (range 10–34). The total bilirubin results were within normal limits and showed no significant change during therapy in any of the children. Serial estimation of AST and gamma GT also demonstrated no change, although one child had mildly increased gamma GT throughout treatment, but normal AST. However, he was receiving phenytoin. Alkaline phosphatase values did not change during treatment in six children. However, after 4 weeks treatment one child, initially with normal ALP, suddenly developed very high values (2832 and 3635 u litre^{-1}), but with no concomitant change in hepatocellular enzymes or any change in medication or clinical status.

In conclusion, in this preliminary study involving small numbers of children we have not demonstrated any evidence of change in hepatic function following repeated daily isoflurane anaesthesia.

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INFLUENCE OF THIOPENTONE ON UPPER AIRWAY MUSCLES

G. B. DRUMMOND
Department of Anaesthetics, Royal Infirmary, Edinburgh

The muscles of the upper airway have an important role in maintaining airway patency and, in laboratory studies, a variety of anaesthetic agents cause more marked depression of the hypoglossal nerve than of the phrenic nerve (Nishino et al., 1984). However, the relative importance of different muscles in maintaining upper airway patency in man has not been established, and the susceptibility of these muscles to depression during anaesthesia is not clear. After consent was obtained, the activities of three groups of muscles in the neck were studied during sedation and anaesthesia with thiopentone in 13 patients about to undergo surgery under general anaesthesia.

Muscle activity was measured by electromyography, using surface electrodes placed below the chin (genioglossus, GG) immediately below the cricoid close to the midline (strap muscles, S), and over the scalene muscles (Sc). The signals were recorded with an FM tape recorder and subsequently replayed through a rectifier and integrator with a time constant of 100 ms, with gating to remove the ECG artefact.

Thiopentone was given in 50-mg doses i.v. at 30-s intervals and EMG activity measured immediately before the next dose was administered. Although there was a general decrease in activity, transient increases in EMG activity were common, particularly in the S and Sc muscles (seven and nine of the patients, respectively). The overall reduction in activity was greater in the GG (log mean reduction to 21 % of awake activity after thiopentone 150 mg).

Transient episodes of airway obstruction occurred in nine of the patients after 250 or 300 mg of thiopentone had been administered. Obstruction was associated with an increase in activity of the strap muscles in eight, the scalene muscles in seven, and the GG in five, followed by a reduction when the obstruction was relieved. This suggests that increased activity in the strap muscles is not sufficient to overcome airway obstruction in these circumstances.

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SPONTANEOUS BREATHING AFTER COMPLETE TETANIC BLOCK BY ATRACURIUM

A. J. ORDMAN* AND J. P. PAYNE
Research Department of Anaesthetics, Royal College of Surgeons of England and St Peter's Hospitals, London

During investigation of the action of small doses of atracurium, it was noted that anaesthetized patients continued to breathe while tetanic stimulation of the adductor pollicis muscle was completely blocked.

This observation was further studied in five unpremedicated patients who had given their informed consent and were about to undergo elective urological surgery.

Anaesthesia was induced with thiopentone 5 mg kg^{-1} and continued with halothane in nitrous oxide, oxygen ($F\mathrm{I}_{\mathrm{O}_2}$ 0.32–0.38) fresh gas flow 70 ml kg^{-1} min^{-1}, via a Magill attachment. Intubation of the trachea was facilitated by topical lignocaine. The halothane concentration was then reduced to 0.5 % for the duration of each study.

A Grass S88 stimulator provided supramaximal stimulation of the ulnar nerve at each wrist at 12-s—50 Hz tetanic stimulation at one wrist and train-of-four (TOF) impulses at the other. Statham transducers were used to measure the force of muscle contractions which were charted on a Brush Clevite recorder.

In addition to routine cardiovascular monitoring, continuous

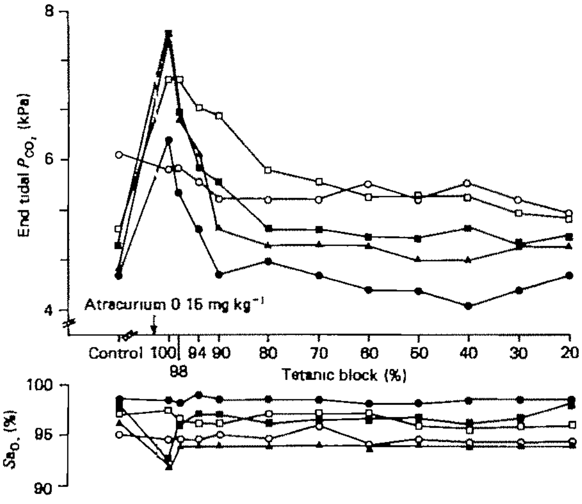

FIG. 1. End-tidal carbon dioxide and arterial oxygen saturation.

measurement of end-tidal carbon dioxide concentration was made using a Datex capnograph carbon dioxide monitor, and an Ohmeda Biox 3700 pulse oximeter was used to record arterial oxygen saturation in the ear lobe.

Three doses of atracurium 0.05 mg kg^{-1} were given i.v. at 2-min intervals.

Complete block of tetanic transmission occurred in each subject, while in none did T1 of the TOF decrease to less than 2% (mean 10.6%) of its control value.

Figure 1 demonstrates that spontaneous ventilation of the lungs remains adequate after doses of atracurium which produce complete tetanic block of adductor pollicis contraction, conditions which are satisfactory for tracheal intubation (Hughes and Payne, 1978).

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POTENCY OF ATRACURIUM AND VECURONIUM AT THE DIAPHRAGM AND ADDUCTOR POLLICIS MUSCLE IN HUMANS

J. R. D. LAYCOCK, F. DONATI* AND D. R. BEVAN
Department of Anaesthesia, Royal Victoria Hospital, Montreal

The diaphragm is relatively resistant to the action of tubocurarine (Wymore and Eisele, 1978) and pancuronium (Donati, Antzaka and Bevan, 1986) when compared with peripheral muscle. This study investigated the relative potencies of atracurium and vecuronium at the diaphragm and adductor pollicis.

Eighteen patients gave informed consent to be studied. After induction of anaesthesia, intubation was accomplished without the use of neuromuscular blockade and anaesthesia was maintained with nitrous oxide, oxygen and halothane. Train-of-four stimulation was applied to the ulnar nerve at the elbow and the right phrenic nerve in the neck. Twitch tension at the adductor pollicis was measured, and the diaphragmatic EMG was recorded through three surface electrodes in the eighth intercostal space. Cumulative dose–response curves were obtained for atracurium 0.1 mg kg^{-1} followed by 0.05-mg kg^{-1} increments, or vecuronium 0.02 mg kg^{-1} followed by 0.01-mg kg^{-1} increments.

This study showed (table II) that approximately one-and-a-half to two times as much atracurium or vecuronium was needed to produce blockade of the same magnitude at the diaphragm as at the adductor pollicis. There was no significant difference between atracurium and vecuronium in their relative potencies at these two sites. The two newer agents appear to exhibit a degree of respiratory sparing comparable to that of longer acting neuromuscular blockers.

TABLE II. *Mean (SEM)* ED_{50} *and* ED_{90} *(*$\mu g\ kg^{-1}$*) at the adductor pollicis (AP) and diaphragm (D), and the D:AP ratio*

	ED_{50}	ED_{90}
Atracurium		
AP	90 (9.1)	133 (9.6)
D	130 (8.6)	245 (17.5)
Ratio	1.56 (0.16)	1.93 (0.29)
Vecuronium		
AP	25 (2.4)	38 (3.6)
D	34 (2.6)	58 (4.7)
Ratio	1.47 (0.16)	1.55 (0.17)

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REQUIREMENTS FOR NEUROMUSCULAR BLOCKING AGENTS DURING PROLONGED ANAESTHESIA IN THE ANAESTHETIZED DOG

D. J. CHAPPLE*, P. DODD*, D. M. MACLEOD*, P. S. WITHINGTON* AND P. M. YATE
Pharmacology I, The Wellcome Research Laboratories, Beckenham; Anaesthetics Unit, The London Hospital Medical College, Whitechapel

A previous study in the ITU with prolonged infusions of atracurium in man suggested that an increase in atracurium requirement develops within the first 72 h (Yate et al., 1985). Our study was designed to determine whether this loss of activity was drug-induced (Matteo and Diaz, 1984) or secondary to prolonged immobilization (Gronert, 1981).

A preliminary study was conducted to demonstrate consistency in producing dose–response curves using five dogs. Anaesthesia was induced with thiopentone and maintained with an infusion of sodium pentobarbitone. The trachea was intubated and mechanical ventilation instituted. Neuromuscular stimulation was performed by percutaneous stimulation of the dog's hind limb by supramaximal train-of-four stimuli delivered every 20 s (Datex relaxograph). The force of contraction of the hindlimb was monitored both by recording the evoked EMG and by using a force displacement transducer (Grass FT10).

Dose–response curves for atracurium were constructed using a dose range of 0.01–0.16 mg kg^{-1} i.v. Values for ED_{50} were calculated using the Gompertz inhibition model. These dogs were allowed to recover and dose–response curves repeated 2 weeks later. There was no significant change ($P = 0.6$) in the ED_{50} values for the dogs between the two occasions and a high correlation ($r = 0.81$) existed between the two methods of measurement.

A further six dogs were studied, using a similar method. Three dogs were allocated to receive an infusion of atracurium for 72 h to maintain the T1 response at 5% of control. The other three dogs received only a pentobarbitone infusion to maintain anaesthesia and immobility. Both groups were ventilated to a normal Pa_{CO_2}. Dose–response curves to

TABLE III. ED_{50} *values from dose–response curves for atracurium at beginning and end of the experiment*

	Control infusion	Atracurium infusion
Before	0.043	0.036
After	0.77	0.063
P	0.009	0.0525

atracurium were constructed at the beginning and end of the experiment, and ED$_{50}$ values calculated (table III).

We conclude that the reduced sensitivity to atracurium seen clinically can also be demonstrated in animals. Our experiments show this to be the result of prolonged immobility rather than of prolonged neuromuscular blockade.

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P6 ACUPUNCTURE: AN EFFECTIVE NON-TOXIC ANTI-EMETIC IN CANCER CHEMOTHERAPY

J. W. DUNDEE, R. G. GHALY AND
K. T. J. FITZPATRICK*
Department of Anaesthetics, The Queen's University of Belfast

Workers from the Belfast Anaesthetic Department have convincingly demonstrated a significant reduction in postoperative sickness in opioid-premedicated patients having 5 min of manual or electro (10 Hz) acupuncture (ACP) at the right P6 (Neiguan) point (Dundee et al., 1986). The reduction of sickness was similar with both forms of ACP and has led to its evaluation in patients having cancer chemotherapy.

In a preliminary study of 71 consecutive patients attending the Northern Ireland Radiotherapy Centre, 54 (76%) had severe sickness following their chemotherapy and 52 of these experienced the same effect with a second course of treatment (Dundee et al., 1987). This study was carried out in patients who had severe sickness following a previous course of treatment, despite the use of metoclopramide.

Crossover study. In random order 10 patients treated with cisplatin for testicular neoplasms received either P6 or "dummy" (point at R elbow) electro ACP at the same time as the chemotherapy. They knew this was an antiemetic study, but did not know about the dummy point. When visited 8 h later, they were asked to compare the degree and duration of sickness with previous experience. There was a marked reduction in sickness with P6, but not with dummy ACP (table IV).

TABLE IV. *Results with P6 and dummy ACP*

ACP	Benefited	No benefit
P6	10	0
Dummy	1	9

TABLE V. *Overall benefit from ACP*

	n	Chemotherapy	Good	Fair
Inpatients	26	Crisplatin Vincristine Bleomycin	13	12
Outpatients	27	Mitozantrone	19	8
	29	Cyclophosphamide Methotrexate 5 Fluorouracil	22	5

P6 study. The overall benefit from ACP in three large groups of patients having P6 ACP alone is given in table V. The ACP was often repeated after 8 h and some patients had five or six treatments. Results are classed as "good" indicating no sickness for 8 h and "fair" indicating a reduction but not complete abolition.

Only three patients failed to obtain any benefit from ACP, from which we encountered no side effects. As practised by us, P6 ACP is time-consuming and needs to be repeated after 8 h. Continuing studies are investigating the use of non-invasive alternatives.

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COMPARISON OF NEUROMUSCULAR RECOVERY FOLLOWING BLOCKADE BY ATRACURIUM, ALCURONIUM AND VECURONIUM FOR GYNAECOLOGICAL LAPAROSCOPY

K. L. KONG* AND G. M. COOPER
Department of Anaesthetics, University of Bristol, Bristol Royal Infirmary

SUXAMETHONIUM—THE RELATION BETWEEN DOSE AND RESPONSE

R. J. CHESTNUT*, T. E. J. HEALY AND
N. J. N. HARPER
University Department of Anaesthesia, University Hospital of South Manchester

There is a wide clinical variation between individuals in the degree of neuromuscular blockade produced by suxamethonium (Walts and Dillon, 1967; Katz and Ryan, 1969), and no study of the response of adults to differing doses, measured electromyographically or mechanically, has been published.

It would, therefore, be instructive to examine the relation between dose and response to suxamethonium using electromyographic measurements and to determine the ED$_{95}$ of the drug.

One hundred and twenty patients (group A) ASA grade I and II, aged 18–65 yr were randomly allocated to one of eight subgroups. Each subgroup received a dose of the suxamethonium normally provided in the anaesthetic room within the range 0.2–0.6 mg kg^{-1}. Neuromuscular transmission was studied by stimulating the ulnar nerve at the wrist, using surface electrodes with a supramaximal square wave impulse of 0.2 ms duration, repeated every 15 s. The evoked compound action potential (ECAP) was amplified and recorded.

A standard anaesthetic technique was used (Black et al., 1985). Ventilation was assisted as required to maintain normocapnia. After stable recordings were established and then maintained for 1 min, three control values of ECAP were recorded. The preselected dose of suxamethonium was then administered i.v., preceded and followed by saline. The ECAP was recorded until maximum blockade was achieved.

The possible role of drug degradation associated with inadvertent storage at room temperature, on the variation in response was studied in 15 patients (group B) who were given 0.3 mg kg^{-1} of suxamethonium which had been refrigerated from manufacture to injection. The body surface area, lean body mass, plasma cholinesterase and time from injection of suxamethonium to fasciculation of the patients in this group were measured.

The ED$_{95}$ of suxamethonium was 0.51 mg/kg body weight with a 95% confidence interval of 63.3% and 99.6%. There was a wide variation in response to each dose. The patients in group B who were given refrigerated suxamethonium 0.3 mg kg^{-1} also showed a wide range of response at that dose (28–98%). However, for these patients the mean block was significantly greater than that obtained using the same dose of normally available suxamethonium ($P < 0.05$).

Body surface area was shown to give a better prediction of response to suxamethonium 0.3 mg kg^{-1} than total body weight ($P < 0.005$). No relation was shown between lean body mass, age or time from injection to fasciculation and response to suxamethonium. The mean maximum blockade occurred 52 s (range 23–98) after the start of fasciculation.

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COMPARISON OF RESPIROMETERS

J. A. DUNPHY*, L. P. CLAFFEY*, W. P. BLUNNIE* AND L. W. CURTIN*

Department of Anaesthesia, Mater Misericordiae Hospital, Dublin

The Gould spirometer, which is based on a pneumotachograph, may give the most accurate measurements of FVC, FEV$_1$ and PEF. In this study we have assessed two cheaper portable spirometers, the Micromedics Pocket spirometer and Vitalograph spirometer and compared the results obtained with those from the Gould.

After ethics committee permission and informed consent, 33 patients were studied. All patients had FVC and FEV$_1$ measured with the Gould spirometer first. After a 5-min rest period, the patients were assessed using the Vitalograph or Micromedics in random sequence, with another rest period between. In all patients, the best of three results obtained with each machine were analysed.

TABLE VI. *Results*

Difference between Gould and	Mean diff. (ml)	SD (ml)	Mean ± 2SD (ml)
Vitalograph			
FVC	−156	260	+364 to −676
FEV$_1$	−209	180	+151 to −569
Micromedics			
FVC	+196	225	+646 to −254
FEV$_1$	+130	246	+622 to −362

Regression analysis is not applicable to this type of data and the method suggested by Bland and Altman was used. The numerical differences between measurements were plotted against the mean of the two values. The mean and standard deviation of these differences were calculated. If the mean ± 2SD were not clinically significant, either method of measurement might be used with confidence.

In general the Vitalograph overreads and the Micromedics underreads with respect to the Gould (table VI). These variabilities are of clinical significance as they represent 10–30% of the normal reading. For approximate preoperative assessment of ventilatory function the Micromedics may be the better portable respirometer to use, as it will present the lowest figures. For precise assessment, the Pulmonary Function Laboratory should be used.

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SEIZURE DURATION AFTER METHOHEXITONE OR PROPOFOL FOR INDUCTION OF ANAESTHESIA FOR ELECTROCONVULSIVE THERAPY (ECT)

K. H. SIMPSON, P. J. HALSALL*, C. M. E. CARR* AND K. G. STEWART*

University Department of Anaesthesia, St James's University Hospital, Leeds

There is good evidence that electroconvulsive therapy (ECT) is an effective treatment for depression (Kendell, 1981). The production of a bilateral convulsion is essential for a therapeutic effect, and it has been suggested that there is a minimum seizure duration necessary for successful treatment (Maletzky, 1978). As patients usually receive several ECT treatments, the quality of anaesthesia is particularly important. Propofol may be of value for ECT anaesthesia, as it has been shown to improve recovery after minor surgery (Kay et al., 1986). The present study was designed to investigate the effect of propofol on seizure duration during ECT in comparison with methohexitone, which is the standard agent.

Ethical Committee approval was granted for the study which involved nine male and 16 female patients, aged 22–81 yr, who were suffering from depressive illness requiring a course of bilateral ECT. Patients gave informed consent to participate in the study, and no patient who was receiving treatment under the provisions of the Mental Health Act was included. Each subject was studied during two separate ECT treatments, when anaesthesia was induced with either methohexitone 1.0 mg kg^{-1} or propofol 1.3 mg kg^{-1} over a period of 20 s, in a random order. Before the administration of suxamethonium 0.5 mg kg^{-1}, the forearm was isolated, by inflation of a cuff to above arterial pressure, so that the seizure duration could be measured. Bitemporal electrodes were used to deliver a 3-s standard shock from an Ectron Duopulse machine. Statistical analysis was by Student's t test for correlated means.

The mean (SD) seizure duration was significantly reduced after propofol (20.7 (13.1) s) compared with methohexitone (35.3 (20.3) s) ($t = 4.81$, $P < 0.01$). Therefore the value of propofol for induction of anaesthesia for ECT may be limited by its adverse effect on seizure duration.

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INFLUENCE OF VOLATILE ANAESTHETIC AGENTS ON THE PHARMACOKINETICS OF MIDAZOLAM

A. J. HEWITT*, J. W. DUNDEE, K. W. HARPER AND P. J. HOWARD
Department of Anaesthetics, The Queen's University of Belfast and the Ulster Hospital, Dundonald

While benzodiazepines can be used to produce light sedation, midazolam has been recommended as an induction agent. It has been noted (Harper et al., 1985) that its pharmacokinetics can be altered by major surgery. As volatile agents are used frequently in balanced anaesthesia (Sarnquist et al., 1980), it would seem necessary to investigate whether such agents, which can have marked effect on haemodynamics, would alter the pharmacokinetics of midazolam.

In 30 unpremedicated healthy women undergoing minor elective gynaecological surgery of 15–20 min duration, anaesthesia was induced with midazolam 0.3 mg kg^{-1} i.v. and maintained with i.v. thiopentone supplement or nitrous oxide in oxygen with enflurane or halothane. Plasma midazolam concentrations were determined by gas–liquid chromatography from serial venous blood samples taken over 12 h. Pharmacokinetic parameters were determined from the plasma concentrations using modelling techniques. Statistical analyses were performed using parametric methods on the logarithmic transformed variables.

Four patients were excluded: two had prolonged elimination half-lives (10+h) and two conformed to a one-compartment pharmacokinetic model. The remaining 26 (table VII) conformed to a two-compartment pharmacokinetic model. Plasma midazolam concentrations were significantly lower in the volatile agent group over the first 2 h following administration. $T_{\frac{1}{2}}^{\beta}$ was similar in both groups but V^{ss} increased significantly in the volatile agent group, as did the volume of distribution in the first compartment. Midazolam clearance increased in the volatile agent group, but not to a significant degree.

TABLE VII. *Pharmacokinetic values in patients receiving a bolus injection of midazolam 0.3 mg kg^{-1} i.v. with or without the use of a volatile anaesthetic agent*

	Control	Volatile agent	P
n	16	10	
$T_{\frac{1}{2}}^{\alpha}$ (min)	15.20	14.40	
$T_{\frac{1}{2}}^{\beta}$ (h)	2.73	2.69	
Clearance (ml kg^{-1} min^{-1})	5.48	7.34	< 0.10
V_1 (litre kg^{-1})	0.37	0.62	< 0.001
V_D^{area} (litre kg^{-1})	1.30	1.71	< 0.5
V^{ss} (litre kg^{-1})	0.90	1.45	< 0.01

The changes found in this study seem likely to result from alterations in blood flow or plasma binding, rather than from enzymatic inhibition. It is interesting to report two further patients had prolonged elimination half-life greater than 10 h (Dundee et al., 1986).

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HEART RATE RESPONSES TO DIFFERENT COMBINATIONS OF EDROPHONIUM AND GLYCOPYRROLATE

P. DODD*, D. GOLDHILL*, D. M. MACLEOD*, P. S. WITHINGTON*, P. M. YATE AND S. DAY*
Anaesthetics Unit and Department of Clinical Epidemiology, The London Hospital Medical College, London

Edrophonium and glycopyrrolate have been proposed as alternatives to neostigmine and atropine during the antagonism of neuromuscular blockade. A previous study (Mirakhur, 1985) found cardiovascular instability with this combination. The aim of this work was to define a dose and administration sequence for edrophonium with glycopyrrolate which would minimize cardiovascular changes.

Sixty adult patients were studied. Following thiopentone, anaesthesia was maintained with nitrous oxide in oxygen and 0.5% halothane. Neuromuscular blockade was obtained with atracurium. Edrophonium and glycopyrrolate were administered at the end of surgery, anaesthesia being continued with halothane/nitrous oxide. All patients received edrophonium 1.0 mg kg^{-1}.

The patients were randomly assigned to four groups: group

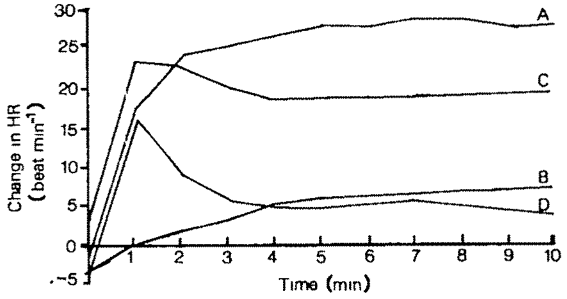

FIG. 2. Changes in heart rate. A = Glycopyrrolate 10 µg kg^{-1} simultaneously with edrophonium 1.0 mg kg^{-1}; B = glycopyrrolate 5 µg kg^{-1} simultaneously with edrophonium; C = glycopyrrolate 10 µg kg^{-1} 1 min before edrophonium; D = glycopyrrolate 5 µg kg^{-1} 1 min before the edrophonium.

A received glycopyrrolate 10 μg kg^{-1} simultaneously with the edrophonium; group B glycopyrrolate 5 μg kg^{-1} simultaneously with the edrophonium; group C glycopyrrolate 10 μg kg^{-1} 1 min before the edrophonium and group D glycopyrrolate 5 μg kg^{-1} 1 min before the edrophonium. The anaesthetist was unaware of the dose of glycopyrrolate. Heart rate, rhythm and arterial pressure (Accutorr) were recorded 2 min before the administration of the glycopyrrolate then at 1-min intervals for 10 min and then at 15, 30 and 60 min afterwards. Halothane was discontinued after the first 10 min.

Arterial pressure and heart rate data from each of the groups were analysed by repeated measures analysis of variance (SPSS).

Both groups given glycopyrrolate 10 μg kg^{-1} showed a significant increase in heart rate ($P < 0.01$), although this was significantly less when glycopyrrolate was administered before the edrophonium (fig. 2). A significantly smaller increase in heart rate was seen in the groups given glycopyrrolate 5 μg kg^{-1}. There was no significant difference between group B and D, although there was a transient increase in heart rate (mean 16 ± SEM 1.7) in the group given glycopyrrolate 5 μg kg^{-1} 1 min before the edrophonium.

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I.V. LIGNOCAINE FAILS TO ATTENUATE THE CARDIOVASCULAR RESPONSE TO LARYNGOSCOPY AND INTUBATION

C. D. MILLER* AND **S. J. WARREN***
Anaesthetic Department, The Grantham Hospital, Aberdeen Hong Kong

I.v. lignocaine has been used to attenuate the cardiovascular response to laryngoscopy and intubation (Mounir, Keszler and Yacoub, 1977; Tam, Chung and Campbell, 1985). We wished to determine the optimal time for its administration.

Forty-five fit Chinese patients were premedicated with morphine 0.2 mg kg^{-1} and hyoscine 4 μg kg^{-1}. Intra-arterial pressure monitoring was established, and anaesthesia was induced with thiopentone 5+1 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1}. Patients were randomly allocated to four groups: a control group and three treatment groups which received lignocaine 1.5 mg kg^{-1} i.v. 1, 2 or 3 min before laryngoscopy. Apart from the rapid bolus dose of suxamethonium and the second dose of thiopentone, all the injections were performed over 30 s. Patients in whom laryngoscopy took longer than 30 s or who had technically poor arterial traces, were excluded from the statistical analysis.

Analysis of variance of heart rates, arterial pressures and rate–pressure products for the remaining 40 patients failed to show a significant difference between the groups. After laryngoscopy, heart rates and arterial pressures were significantly higher than the pre-induction control values. Study variables were rigidly controlled by studying only fit patients not receiving drugs affecting the cardiovascular system, using intra-arterial pressure monitoring, giving the drugs in a standardized manner, and studying one ethnic group; Chinese patients may have slightly different cardiovascular responses compared with others (Rodrigo, Moles and Lee, 1986). Previous studies did not control all these variables.

We conclude that, in this situation, pretreatment with lignocaine 1.5 mg kg^{-1} i.v. does not attenuate the response to laryngoscopy and intubation.

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USE OF DIFFUSIVE SAMPLERS TO MONITOR OCCUPATIONAL EXPOSURE TO WASTE ANAESTHETIC GASES

W. M. GRAY*, J. O'SULLIVAN*,
H. B. HOULDSWORTH* AND N. MUSGRAVE*
Department of Clinical Physics and Bio-Engineering, West of Scotland Health Boards, Glasgow; and Departments of Pharmacy and Anaesthetics, Barnsley District General Hospital

We have investigated the suitability of Perkin–Elmer's tube-type diffusive sampler (Houldsworth, O'Sullivan and Musgrave, 1982; Cox and Brown, 1984) for monitoring exposure to waste anaesthetic gases.

The tubes for nitrous oxide adsorption were packed with molecular sieve 5A and those for volatile anaesthetic agents with Tenax TA. After exposure, the samplers were analysed by automatic thermal desorption and gas chromatography. Uptake rates and sampling repeatability were measured by exposing batches of samplers to various test atmospheres for 1, 2, 4 or 8 h. Repeatability in practice was assessed by analysing duplicate nitrous oxide samplers worn by operating theatre staff. Storage characteristics were investigated by analysing batches of six samplers at 0, 14 and 28 days after a test exposure to nitrous oxide. The sealing efficiency of the storage caps was also assessed by exposing batches of capped nitrous oxide samplers to a test atmosphere for 1 h. The ease of use of the samplers has been assessed during the collection and processing of more than 5000 samples from locations throughout the U.K.

The uptake rate was independent of concentration, but decreased with increasing exposure time, as follows:

$$\text{Uptake rate}/(\text{ng p.p.m.}^{-1}\ \text{min}^{-1}) = a\ (\text{time/h})^{-b}$$

where $b = 0.16$ for nitrous oxide and 0.18 for the volatile agents, and $a = 1.44$, 3.32, 2.94 and 2.82 for nitrous oxide, halothane, enflurane and isoflurane, respectively. The coefficients of variation (CV) for laboratory and theatre exposures of the nitrous oxide samplers were 4.6% (78 d.f.) and 10.9% (20 d.f.), respectively. The CV for laboratory exposures of the volatile agent samplers was 5.5% (70 d.f.). The mean amounts of nitrous oxide recovered from the tubes stored for 14 and 28 days were 93.1% and 90.0%, respectively, of the 0-day value. The 28-day value was significantly less than the 0-day value at the 0.05 level (one-sided Wilcoxon test). Ten tubes fitted with storage caps with new O-rings showed a mean nitrous oxide uptake of 1.4% (range 0–2.9%) of the uptake expected for tubes fitted with sampling caps. For 10 tubes the caps of which had been fitted and removed 50 times without renewing the O-rings, the mean uptake was 6.8% (range 2.5–13.4%) of the sampling uptake. No major problems have been experienced during routine use of the samplers.

We conclude that the performance of the samplers is adequate for routine monitoring of occupational exposure to waste anaesthetic gases. However, the design of the storage caps is poor, and care must be taken to avoid contamination during storage and transport.

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ANALGESIC EFFECTS OF BUPIVACAINE I.P.

R. P. ALSTON*, H. OWEN, M. BELL* AND H. BURNS*
University Departments of Anaesthesia and Surgery, Royal Infirmary, Glasgow

Wound infiltration with bupivacaine has been shown to reduce the opioid consumption following cholecystectomy (Patel et al., 1983). The aim of this study was to investigate whether i.p. instillation of bupivacaine had a similar effect.

In a double-blind study, 20 patients scheduled for elective abdominal surgery were allocated randomly to either control or bupivacaine groups. Both groups were stratified by age of 55 yr and anaesthesia was standardized. On incision of the peritoneum, 0.9 % sodium chloride 100 ml with or without bupivacaine 1 mg kg^{-1} was instilled and, 2 h later, an i.p. infusion of 0.9 % sodium chloride 500 ml with or without bupivacaine 3 mg kg^{-1} was commenced at 83 ml h^{-1}.

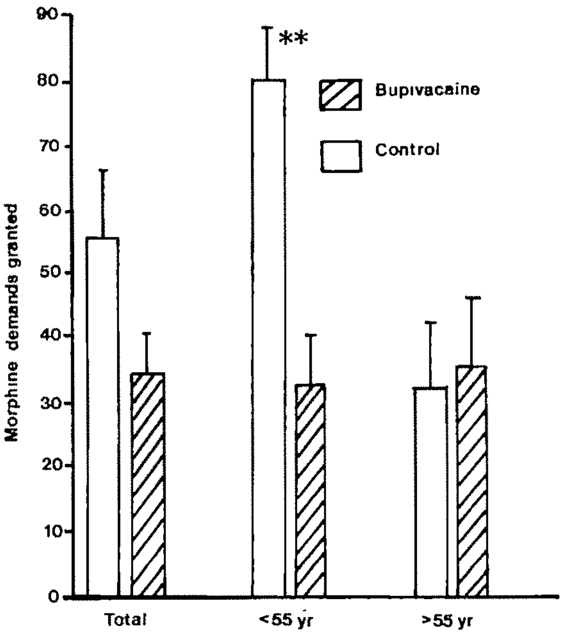

FIG. 3. Cumulative morphine demands granted at 24 h after i.p. instillation of bupivacaine. $^{**}P < 0.01$.

Pain and nausea scores (verbal rating scale) were recorded before operation and at 8 and 24 h following initial instillation. Blood samples were taken after induction and at 1 and 8 h after instillation and were later analysed for plasma bupivacaine (gas chromatography). Morphine was administered i.v. by patient controlled analgesia and cumulative demands recorded.

No significant differences were found in age and weight nor pain or nausea scores between the groups. In the control group at 24 h, morphine demands were significantly greater ($P < 0.05$) in younger than in older patients (fig. 3).

Younger patients receiving bupivacaine had significantly less morphine demands than those who did not ($P < 0.01$), whereas in older patients there was no significant difference between groups. Plasma concentrations of bupivacaine were 273 ng ml^{-1} (SD 200) at 1 h and 658 ng ml^{-1} (SD 431) at 8 h.

I.p. bupivacaine reduced analgesic requirements following abdominal surgery in younger patients, but not older ones.

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INTRA-ABDOMINAL PRESSURE SWINGS DURING BREATHING REFLECT CHANGES IN ABDOMINAL MUSCLE ACTIVITY AFTER ABDOMINAL SURGERY

J. DUGGAN* AND G. B. DRUMMOND
Department of Anaesthetics, Royal Infirmary, Edinburgh

Abdominal muscles show phasic expiratory activity following upper abdominal surgery. To investigate the effect of this pattern of abdominal muscle activity on intra-abdominal pressure we have studied a further four patients making simultaneous recordings of the integrated abdominal muscle electromyogram (E_{ab}), intra-gastric pressure (P_{ga}) and nasal air flow.

Patients studied underwent elective biliary or gastric surgery via a right upper quadrant incision and with a standard anaesthetic technique. Measurements were made 3–6 h after surgery. Intra-gastric pressure was measured with a pressure transducer connected to a nasogastric tube perfused with saline at 10 ml h^{-1}. Abdominal muscle activity was measured by electromyography (EMG), using a pair of surface electrodes placed 2 cm below the left costal margin in the mid clavicular line with their centres 4 cm apart. Nasal air flow was measured using nasal cannulae acting as two single pitot tubes connected in parallel to give a signal of flow (Guyatt, Parker and McBride, 1982). The direct EMG, P_{ga} and nasal airflow signals were recorded on FM magnetic tape and replayed on a u.v. recorder. The direct EMG signal (bandwidth 20–2 kHz) was rectified and integrated as an exponential average (E_{ab}) with a time constant of 100 ms. Thirty consecutive breaths in each patient were subject to detailed analysis. The detection of the start and end of inspiratory and expiratory flow allowed three parts of each breath to be analysed separately. I = inspiration; E = expiration; EP = expiratory pause.

Each patient showed a mostly phasic pattern of abdominal muscle activity during quiet tidal breathing, with short episodes of tonic activity caused by postural adjustment or arousal. Intra-gastric pressure traces closely resembled traces

TABLE VIII. *Relationship between change in* E_{ab} *and changes in* P_{ga}. *Linear regression correlation coefficients.* *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

Patient	I	E	EP
1	0.72***	0.63***	0.46*
2	0.73***	0.6***	0.68***
3	0.84***	0.57**	0.56**
4	0.8***	0.56**	0.62***

of abdominal muscle activity. The relationship between changes in E_{ab} and P_{ga} in each part of the ventilatory cycle was assessed using linear regression analysis (table VIII).

This pattern of abdominal muscle activity after upper abdominal surgery clearly has an important influence on intra-abdominal pressures during breathing. On the basis of changes in the relative pleural and abdominal pressure swings after abdominal surgery, other investigators (Ford et al., 1983) have suggested that diaphragmatic function is impaired. Because the contribution of the abdominal muscles has been ignored, this is not a valid conclusion.

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PHARMACOKINETICS OF ORAL NALBUPHINE IN POSTOPERATIVE PATIENTS

B. KAY, J. ORTON*, **J. HINDMARSH*** AND A. LAKE*
Department of Anaesthesia, University Hospital of South Manchester, Manchester

The purpose of this study was to obtain pharmacokinetic data for nalbuphine administered by mouth to postoperative patients and to relate pain gradings to plasma concentrations.

Pharmacokinetic data for nalbuphine administered by mouth and i.v. to healthy volunteers have already been published by Aitkenhead, Lin and Achola (1986).

Ten patients, three female, mean age 22.8 yr (range 17–33) and of mean weight 66.2 kg (range 50–80) were studied after oral surgery.

Each patient received a premedication of diazepam 10 mg by mouth 2 h before surgery. Thiopentone 4–5 mg kg^{-1} and suxamethonium 1 mg kg^{-1} were given through an i.v. cannula. Nasal intubation was performed. Anaesthesia was maintained using clinically appropriate concentrations of nitrous oxide and enflurane in oxygen with the patient breathing spontaneously through a Mapleson "A" system. No opioid or other analgesic was given before recovery of consciousness. Immediately on recovery of consciousness the patients were asked to indicate the intensity of their pain on a 10-cm linear analogue scale and a blood sample was taken through an i.v. cannula. The patients then received 60 mg of nalbuphine as their first analgesic. Further blood samples were taken at 15, 30, 45, 60, 90, 120, 180, 240, 360, 480 and 1440 min after medication.

TABLE IX. *Pharmacokinetic data*

Parameter	Mean	Range
$T_{\frac{1}{2}}$ (min)	242.1	102.4–411.4
C^{max} (ng ml^{-1})	32.5	9.0–69.0
T^{max} (min)	106.9	15.0–240.0

The samples were put into lithium heparin tubes, centrifuged and the plasma stored at −20 °C before analysis. Plasma nalbuphine was measured by high performance liquid chromatography (Keegan and Kay, 1984).

Pain was assessed at 30, 60, 120, 180 and 240 min. If additional analgesia was given the time of administration was recorded. Blood samples continued to be taken, but no further pain gradings were made.

The logarithm of the plasma concentration for those subjects who had received no additional analgesia ($n = 7$) was plotted against time and the data subjected to least squares regression analysis. The following pharmacokinetic data were derived: half-life, maximum concentration of nalbuphine and time to achieve maximum concentration (table IX).

Nine patients had detectable nalbuphine in the plasma at 24 h. The relation between pain gradings and the plasma nalbuphine was not consistent.

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VOLTAROL (DICLOFENAC) AS A PERIOPERATIVE ANALGESIC SUPPLEMENT

D. R. DERBYSHIRE AND J. RICHARDSON
Warwick Hospital, Warwick

Opioids remain the mainstay of postoperative analgesia in the U.K. They are beset by unwanted effects many of which are dose related.

TABLE X. *Results (mean (±SD)).* *$P < 0.05$ *(Wilcoxon test)*

	Placebo ($n = 14$)		Diclofenac ($n = 12$)
Age (yr)	40.6 (8.6)		43.5 (7.4)
Weight (kg)	69.1 (17.8)		73.3 (14.6)
Premedication to 1st assess. (min)	290 (60)		270 (50)
Induction to 1st assess. (min)	125 (40)		125 (40)
Papaveretum (mg)			
1 In recovery	7.2 (7.4)	ns	4.2 (4.7)
2 0–12 h	26.8 (10.5)	*	14.2 (10.8)
3 13–24 h	22.1 (12.6)	ns	22.5 (10.1)
Mean pain score			
Recovery	2.4 (0.8)	*	1.6 (0.9)
24 h	1.8 (0.9)		1.5 (0.7)

Non-steroidal anti-inflammatory drugs (NSAID) have long been used to augment the opioid analgesics used in cancer pain. It has been our practice to administer a suppository of an NSAID during the perioperative period to provide better analgesia after operation.

This study was designed first to quantify any benefit from such a suppository administered in the immediate postoperative period, and second to see if NSAID administered at the time of premedication provides any detectable analgesia after major abdominal surgery.

Otherwise healthy women about to undergo major abdominal gynaecological surgery gave written informed consent to participate in this randomized double-blind study which had been approved by the District Ethics Committee. Excluded from the study were those who were allergic to any NSAID, those with any history of peptic ulceration, coagulation disorder or likelihood of continuing pregnancy.

Two or more hours before operation, diazepam 10–15 mg was administered by mouth together with magnesium trisilicate mixture 30 ml and either diclofenac 50 mg or matched placebo.

Anaesthesia was induced with thiopentone and neuromuscular blockade established with vecuronium. Papaveretum 15–20 mg i.m. was administered in the anaesthetic room. The operation was conducted while the patients were ventilated (PE'_{CO_2} 4.5–5.5 kPa) with approximately 66% nitrous oxide in oxygen supplemented with enflurane.

Thirty minutes after antagonism of residual neuromuscular blockade patients were asked to rate their pain on a five-point scale. Papaveretum was then administered i.v. until the patient required no more or 20 mg had been given (whichever was the lesser). The suppository was then administered (either diclofenac 100 mg or placebo) and the patient returned to the ward. Papaveretum 15 mg was prescribed 2 hourly as needed. Approximately 24 h after operation, the amount of papaveretum administered to each patient was determined and the patients were asked to rate the quality of their pain over the preceding 24 h. Results are shown in table X.

It is concluded that concurrent administration of this NSAID lowers the perioperative requirements for opioid analgesia. The perioperative administration of diclofenac is worthy of further study.

THE LOCKOUT INTERVAL IN PATIENT-CONTROLLED ANALGESIA: A RATIONAL BASIS FOR CHOICE?

H. OWEN, L. E. MATHER*, W. B. RUNCIMAN*, R. J. CARAPETIS* AND R. N. UPTON*
Department of Anaesthesia and Intensive Care, Flinders Medical Centre, Bedford Park, South Australia

In patient controlled analgesia, the agent chosen influences the values chosen by the prescriber for the other system variables,—that is the size of the increment and the duration of the lockout interval. The optimal increment provides adequate analgesia whilst avoiding adverse effects; the lockout interval provides a safeguard against accumulation of drug before appreciation of the effects of the previous dose. Attempts have been made to ascertain optimal increments empirically, but there remains diversity of opinion (Bennett, 1986; Rosen, 1986). There is a notable absence of reports of studies on the lockout interval.

Although it is not possible to measure the concentrations of opioids at their receptors *in vivo*, the distribution of drug between blood and brain can be quantitated in suitable animal preparations. Bolus doses of morphine, alfentanil, or both were injected to the right atrium of chronically cannulated sheep (Runciman et al., 1984); blood samples were obtained for drug assay from catheters resident in the aorta and sagittal sinus and cardiac output was measured by thermodilution. The rate of drug distribution (flux) between blood and brain was determined from the product of estimated brain blood flow (2% of cardiac output) and arterio-venous drug concentration gradient (fig. 4).

The corresponding mass of drug in the brain may be determined from the difference in areas under the arterial and venous blood drug concentration–time curves. As long as the flux remains positive, there is net movement of drug from blood to brain and the concentration in the brain and, presumably, the drug effect, are still increasing. Additional doses can be administered after the flux has become negative and brain concentrations begin to decrease, since the maximal effect of the first dose should have been achieved. This information could not be deduced from study of systemic blood concentrations alone. We believe that the duration of positive flux may provide a rational basis for setting the lockout interval.

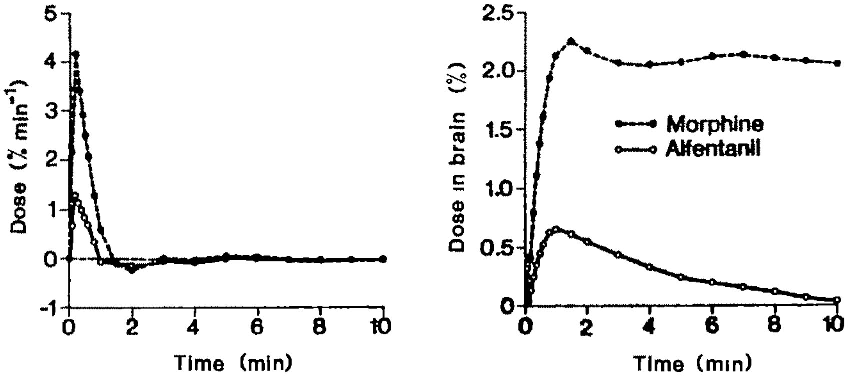

FIG. 4. Distribution of drugs with time.

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DO PATIENTS FASTING BEFORE AND AFTER SURGERY RECEIVE THEIR PRESCRIBED MEDICATION?

R. WYLD* AND W. S. NIMMO
Department of Anaesthesia, University of Sheffield

Many patients undergoing surgery take medication concurrently. Abrupt withdrawal of some of these drugs may be harmful. We have studied patients before and after surgery to identify if they received their prescribed medications.

Over a period of 3 months, we recorded all drugs prescribed and administered to 170 patients, admitted consecutively to one of two general surgical wards. Observations were made on the day of surgery and again the following day. The total number of single prescriptions, the number omitted and the reasons for any omissions were recorded.

Of 170 admissions, 147 were elective, six were emergencies, 12 were GP referrals, and five were transfers from other wards. Of these 170 patients, 72 (42 %) were prescribed concurrent medication unrelated to the surgery or anaesthesia. There were 1756 single prescriptions in the 2 days (> 10 per patient) (table XI). Of these, 854 were analgesics and premedications which were all given as prescribed. Two hundred and fifty-nine (15 %) prescriptions were omitted.

In the cardiovascular group 39/100 prescriptions were omitted including 8/22 betablockers, 9/15 antihypertensives and 6/20 vasodilators. In the respiratory group, 36/108 bronchodilators were omitted and in the endocrine group, 4/12 thyroid drugs and 6/43 corticosteroids were not given. The reasons given for the omission of 67 % of prescriptions was "patient fasting". For the remainder, no reason was given. Nebulized and parenterally administered drugs were amongst those omitted.

In summary, 15 % of all prescribed drugs were omitted on the day of surgery or 1 day after. This was not known to the medical staff. If one excludes analgesics and premedications which were all given, 29 % of prescribed drugs were omitted. This may introduce a variability in patient response to the perioperative period.

TABLE XI. *Analysis of medication prescribed. Drug groups allocated according to B.N.F.*

Drug groups	Total	(%)	No. omitted	(%)
GI	40	(2)	31	(78)
CVS	100	(5.5)	39	(39)
Respiratory	108	(6)	36	(33)
CNS	73	(4)	36	(49)
Infection	255	(15)	32	(13)
Endocrine	61	(3.5)	10	(16)
Urinary tract	6	(0.5)	3	(50)
Malig. disease	9	(0.5)	4	(44)
Nutrition and blood	33	(1.5)	24	(71)
Musculo-skeletal	56	(3.5)	28	(50)
Antithrombotics	161	(9)	16	(10)
Premeds and analgesics	854	(49)	0	(0)
Total	1756	(100)	259	

EFFECT OF PREOPERATIVE ORAL FLUID ON HUNGER AND THIRST

J. R. MALTBY, **A. HUTCHINSON**,
A. D. SUTHERLAND, J. P. SALE AND C. R. G. REID
Department of Anaesthesia, Foothills Hospital at the University of Calgary

Approximately one-half of all elective daycare surgical patients who fast from midnight suffer moderate or severe hunger and thirst (Sutherland, Stock and Davies, 1986). To assess the effect of fluids taken by mouth 2–3 h before surgery on patient's hunger and thirst, 540 healthy adults between the ages of 18 and 60 yr were randomly allocated to one of four groups.

Patients who were receiving drugs known to affect gastric secretion or motility, or for whom an opioid or anticholinergic premedication was ordered, were excluded. All patients were interviewed 2–3 h before surgery, and informed consent obtained. Immediately after the interview they received water, coffee or orange juice 150 ml with ranitidine 150 mg by mouth (group I) or placebo (group II); ranitidine alone (group III); or placebo alone (control). Patients graded their hunger and thirst on a scale of 1 (nil) to 4 (severe) at the time of interview and again on arrival in the operating theatre. Changes in symptoms for each patient (table XII) were obtained from differences between the two scores.

TABLE XII. *Changes in hunger and thirst with oral fluids or continued fast*

		Hunger			Thirst		
	n	Less	More	Same	Less	More	Same
Group I	160	29	43	88	74	12	74
Group II	160	48	34	78	74	11	75
Group III	110	21	36	53	33	27	50
Control	110	16	25	69	19	27	64

There were no statistically significant differences between the fluid groups (I and II) and the fasting groups (III and control) with respect to changes in hunger ($\chi^2 = 4.2$, $P > 0.1$). However, there was a significant reduction in thirst between the fluid and fasting groups ($\chi^2 = 46.3$, $P < 0.001$). The ranitidine groups (I and III) and the placebo groups (II and control) showed no differences in either hunger or thirst ($P > 0.1$). Mean gastric fluid volumes after induction of anaesthesia were: group I 13.2 ± 14.2 ml; group II 22.1 ± 18.3 ml; group III 9.6 ± 10.8 ml; control 25.8 ± 18.5 ml. pH was significantly greater in the ranitidine groups, but unaffected by oral fluid. Fluids taken by mouth 2–3 h before surgery reduce preoperative thirst without affecting gastric fluid volume or pH at the time of surgery.

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SUBARACHNOID ANAESTHESIA WITH SOLUTIONS OF DIFFERING BARICITY

A. LEE*, D. RAY*, D. G. LITTLEWOOD AND J. A. W. WILDSMITH
Department of Anaesthetics, Royal Infirmary, Edinburgh

The specific gravity of a local anaesthetic solution is one of the most important factors affecting subarachnoid spread (Brown et al., 1980). Hyperbaric solutions are usually made with concentrations of dextrose in the range 5–8%, and produce blocks with a mean upper level of analgesia of T5–6. Extensive sympathetic blockade may be a problem. Isobaric solutions do not guarantee a high enough blockade for many operations and the ideal solution would produce blockade with a mean level of T8. This double-blind study was designed to investigate whether hyperbaric solutions of specific gravity closer to CSF than solutions at present in use would achieve this objective.

Forty patients underwent subarachnoid anaesthesia at L3–4, using amethocaine solutions prepared by dissolving a crystalline preparation in different proportions of 0.9% saline and 5% dextrose. This gave solutions containing 0%, 1.25%, 2.5% and 5% dextrose, and a constant amethocaine dose (10 mg) in 2 ml. Four groups of 10 patients were randomly allocated to receive one of these solutions. Solutions were injected while the patient was in the right lateral position and thereafter remained horizontal and supine. Analgesia and anaesthesia, motor power, heart rate and arterial pressure were assessed at regular intervals for 30 min. Comparisons were made using Kruskal–Wallis and Mann–Whitney tests.

The mean maximum height of block was greater in the hyperbaric groups (T6–7) compared with the isobaric group (T11). At each assessment the height of block was significantly greater in the hyperbaric groups than in the isobaric group, except at 2 min, when the 1.25% dextrose solution behaved more like the isobaric solution. The times to maximum blockade were the same in all groups. The times to analgesia and anaesthesia at T12 were significantly shorter in all the hyperbaric groups and paralysis of the legs occurred faster in the hyperbaric groups, although this just failed to reach statistical significance. Hypotension required treatment only in the hyperbaric groups. One patient in the isobaric group had inadequate analgesia.

Solutions made only slightly hyperbaric behaved in a manner almost identical to solutions of much greater specific gravity. The rate of onset may be influenced by baricity, the solution containing 1.25% dextrose behaving more like the isobaric solution for the first 2 min. It is not apparent why hyperbaric solutions currently available have a specific gravity and tonicity far exceeding that of CSF, as this would appear to be unnecessary.

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EFFECTS OF GENERAL ANAESTHESIA ON REACTION TIME IN ELDERLY PATIENTS UNDERGOING ENDOSCOPIC UROLOGICAL SURGERY

C. M. SMITH, M. CARTER, B. LOUGHNAN, R. MARKS, P. S. SEBEL, AND P. M. YATE
Departments of Pharmacology & Therapeutics and Anaesthetics Unit, The London Hospital Medical College, London

Reaction time is impaired for up to 48 h in middle-aged patients undergoing hernia repair with general anaesthesia (Herbert et al., 1983). We have undertaken a similar study in older patients undergoing endoscopic urological surgery.

Patients were premedicated with temazepam 20 mg by mouth 1 h before operation. Anaesthesia was induced with thiopentone and maintained with nitrous oxide in oxygen and halothane or enflurane. Alcuronium was used for neuromuscular blockade for procedures expected to last longer than 20 min; otherwise the patients breathed spontaneously. On the day before surgery, patients were screened using the Clifton Assessment Procedure for the Elderly (CAPE) (Pattie, 1981) to assess orientation and memory, and a four-choice visual reaction time test which separated reaction time from motor time. Reaction time was re-tested 1, 2 and 3 days after surgery. Orthopaedic patients at least 12 days post-surgery served as controls. Data are presented as mean ± SEM and statistical analysis was with Student's *t* tests.

A preliminary study indicated that there was no significant difference in change of reaction time scores from baseline to 24 h after surgery between nine anaesthetized patients (mean age 62 yr) and 10 orthopaedic patients (mean age 56 yr), both scoring the maximum score of 12 on the CAPE (table XIII). Three additional patients aged 83 yr, 69 yr and 65 yr, with imperfect CAPE scores of 9, 10 and 10, showed large increases in reaction time scores of 1258 ms, 119 ms and 119 ms 24 h after surgery; these were well outside the 95% confidence limits of the other anaesthetized patients.

In a follow-up study in 33 patients (mean age = 71 yr; range = 51–85 yr), to examine factors contributing to postoperative impairment, there was no significant difference in change of reaction time scores from baseline to 24 h after surgery, between patients of median age, 73 yr and below (*n* = 19) and those above the median age (*n* = 14). These data suggest that advanced age *per se* does not predispose to marked postoperative impairment of reaction time.

TABLE XIII. *Reaction time scores (ms) (70 trials).* **95% confidence limits from −38.6 to 2.4 ms*

	Day before surgery	24 h after surgery	Difference score
Anaesthetized patients ($n = 9$)	378±31	360±25	−18±8*
Control ($n = 10$)	349±14	336±10	−13±11

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COMPARISON OF SUBANAESTHETIC CONCENTRATIONS OF ISOFLURANE AND NITROUS OXIDE IN VOLUNTEERS

I. M. McMENEMIN AND G. D. PARBROOK
University Department of Anaesthesia, Royal Infirmary, Glasgow

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CISAPRIDE IS MORE EFFECTIVE THAN METOCLOPRAMIDE IN PREVENTING MORPHINE-INDUCED DELAY IN GASTRIC EMPTYING

P. A. BAMBER*, D. J. ROWBOTHAM* AND W. S. NIMMO
Department of Anaesthesia, University of Sheffield

Cisapride (a gastric prokinetic drug) prevents morphine-induced delay in gastric emptying. The present study has compared the effects of metoclopramide and cisapride on morphine-induced gastric delay.

After Ethics Committee approval and informed consent, 40 surgical patients were allocated randomly to receive one of the following premedications i.m.: group A placebo only; group B morphine 10 mg + placebo; group C morphine 10 mg + metoclopramide 10 mg; group D morphine 10 mg + cisapride 10 mg.

Gastric emptying was assessed using the rate of absorption of paracetamol 1.5 g taken by mouth with water 50 ml, 20 min after the premedication. Blood for paracetamol analysis was taken at 15-min intervals for 90 min.

Absorption was estimated from the concentrations at each time point, and by the areas under the concentration curves (AUC) from zero to 45, 60 and 90 min.

Thirty-seven patients were included in the final analysis.

Statistical analysis was by one-way analysis of variance and Kruskal–Wallis non-parametric analysis of variance with rank sum difference analysis where appropriate.

There were no significant differences between the four groups in respect of age, weight or sex.

At 60 and 90 min there was a significantly greater AUC in group D compared with group B or C. At 90 min there was a significantly smaller AUC in group B compared with group A (table XIV).

At 45, 60, 75 and 90 min, paracetamol concentrations were significantly greater in group D compared with group B or C, and significantly lower in group B compared with group A. At 75 and 90 min, paracetamol concentrations were significantly greater in group C compared with group B (not tabulated).

These results support existing evidence that cisapride significantly increases the rate of paracetamol absorption in patients given morphine. These results also suggest that cisapride is more effective than metoclopramide in increasing the rate of paracetamol absorption in these patients.

TABLE XIV. *Mean (±SEM) areas under the plasma paracetamol concentration curve for each group. *Significantly different from group D; **significantly different from group B* ($P < 0.05$)

	Time (min)		
	45	60	90
Group A	421	638	1065
($n = 9$)	(±131)	(±152)	(±194)**
Group B	226	337	566
($n = 9$)	(±72)	(±90)*	(±125)*
Group C	351	513	848
($n = 10$)	(±122)	(±154)*	(±203)*
Group D	614	895	1414
($n = 9$)	(±106)	(±120)	(±131)

EFFECT OF DIAZEPAM ON POTASSIUM FLUX IN BURNS PATIENTS FOLLOWING THE ADMINISTRATION OF SUXAMETHONIUM

G. EARNSHAW, N. SONI* AND A. H. LANDES*
Magill Department of Anaesthetics, Westminster and Queen Mary's Hospital, London

Diazepam is known to decrease the increase in serum potassium (K^+) following suxamethonium administration (Eisenberg, Balsey and Katz, 1979). This study was undertaken to observe the K^+ flux in burns patients, following suxamethonium with and without pre-administration of diazepam. Suxamethonium was routinely used for intubation in this unit, despite observations on K^+ flux (Finer and Nylen, 1961).

Seven adults, who gave informed consent for this study, had a 10% or greater area of full thickness burns and were between 10 and 42 days post trauma.

Each patient in this study needed two anaesthetics. Before the first they were randomly assigned to two groups. Group 1 received pretreatment with diazepam before administration of suxamethonium, whereas group 2 did not. In the second anaesthetic, the patient acted as his own control. In both groups premedication consisted of papaveretum and hyoscine 1 h before operation. A central venous cannula was inserted under local anaesthetic before induction of anaesthesia with thiopentone followed by suxamethonium 1 mg kg^{-1}. Anaesthesia was maintained via a tracheal tube with nitrous oxide–oxygen–enflurane and ventilation assisted to maintain end-tidal $P\text{co}_2$ at 5%. In the group receiving pretreatment, Diazemuls 0.05 mg kg^{-1} was administered 5 min before suxamethonium. Blood was withdrawn via the central catheter for estimations of serum K^+ before induction and 3, 6 and 15 min after administration of suxamethonium. Statistical analysis of the two groups at the four times (baseline, 3, 6 and 15 min) was by a simple analysis of variance with a t test on any grouping with significant variance.

There were significant increases in K^+, from base line, for both groups 3, 6 and 15 min after suxamethonium. The group receiving suxamethonium alone had the greatest increase. This occurred at 3 min and was of 1.2 ± 0.2 mmol (mean ± SEM). Following diazepam pretreatment, the increase in K^+ concentration at 3 min (0.5 ± 0.1 mmol) and 6 min (0.4 ± 0.07 mmol) after suxamethonium was significantly less than in the unpretreated group.

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RENAL PERFUSION DURING AMINO ACID INFUSION IN THE PIG

R. KIPLING*, D. ST J. COLLIER* AND P. J. MORRIS
Departments of Anaesthetics and Surgery, Addenbrooke's Hospital, Cambridge

Protein intake releases hepatic glomerulopressin which increases the perfusion of both superficial and deep nephrons; renal blood blow and glomerular filtration rate (GFR) increase, resulting in the leakage of protein into the mesangium with subsequent sclerosis and loss of functioning nephrons (Brenner, Meyer and Hostetter, 1982). GFR, estimated by creatinine clearance, was increased in patients during the infusion of an isotonic amino acid solution, when compared with 0,9% saline (Collier et al., 1986). We compared the influence of i.v. infusions of either isotonic amino acid solution or 4% dextrose–0.18% saline solution on superficial and deep renal cortical perfusion in pigs.

Superficial and deep cortical renal blood flows were measured by the hydrogen clearance technique using implanted platinum electrodes in 12 normothermic Large White pigs, anaesthetized and ventilated to normocapnoea. Initially all animals received an i.v. infusion of Hartmanns solution 4 ml kg^{-1} h^{-1}; mean arterial pressure (MAP), arterial blood-gas tensions and renal blood flows were measured. Each animal then received a randomly allocated i.v. infusion, 4 ml kg^{-1} h^{-1}, of either 4.25% amino acid solution (six animals) or 4% dextrose–0.18% saline solution (six animals). These infusions were maintained for 210 min, then abruptly discontinued and returned to the control infusion regimen for 60 min. MAP was measured continuously and renal blood flow measurement and blood-gas analysis performed every 30 min throughout the experiment.

There were no significant changes in MAP or blood-gas parameters throughout the experiments. Superficial cortical blood flow was significantly decreased at 180 min ($P < 0.05$) during both amino acid and dextrose–saline infusions and deep cortical flow was significantly increased at 150 min ($P < 0.05$) during amino acid infusion (fig. 5).

The decrease in superficial flow during infusion of the test solutions and the subsequent return to control values may result from differences in sodium ion (Na^+) concentration (Hartmanns solution 138 mmol litre^{-1}; dextrose–saline and isotonic amino acid solution 30 mmol litre^{-1}), as infusion of Na^+ causes an increase in total renal blood flow (Nashat, Tappin and Wilcox, 1976).

The increase in deep blood flow during isotonic amino acid infusion may be caused by release of glomerulopressin from the liver (Brenner, Meyer and Hostetter, 1982) and may explain the increase in GFR demonstrated in humans (Collier et al., 1986).

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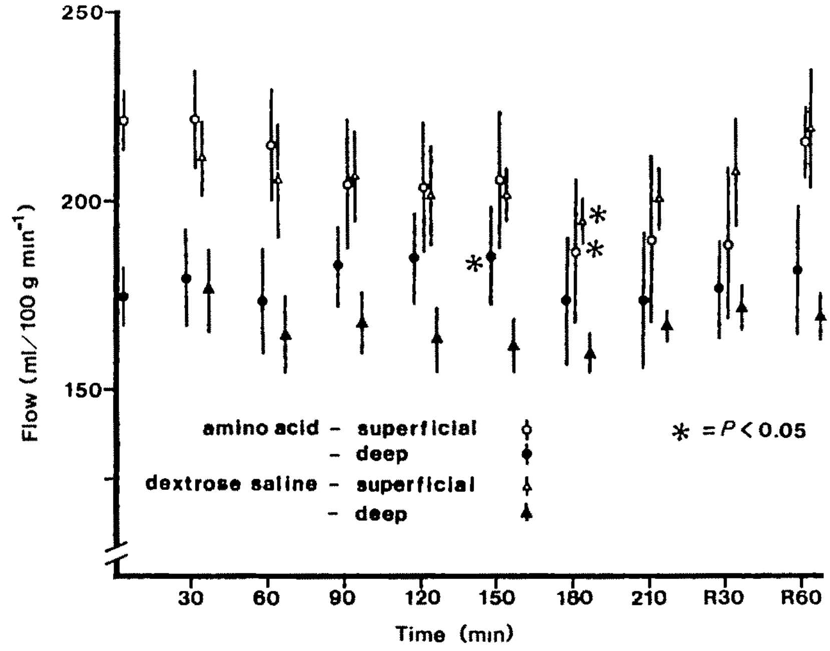

FIG. 5. Changes in renal blood flow (±SEM). First pair of values = control.

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CORRESPONDENCE

UNCONSCIOUS PERCEPTION DURING GENERAL ANAESTHESIA

Sir,—Whether a patient can store memories during anaesthesia is fundamentally important to our conception of what is anaesthesia. It is, therefore, regrettable that publications that make startling claims do not provide adequate evidence because of statistical and methodological shortcomings.

Bonke and colleagues (1986) believe that positive auditory suggestions during an operation can lead to a shorter postoperative stay in hospital in older patients. It is, however, not particularly surprising that they have found one "significant" comparison, since they have carried out 14 separate statistical tests on the outcome data. A rough rule in this situation is to multiply the obtained P value by the number of tests, and this would produce a corrected P value of $0.004 \times 14 = 0.056$ which is not so impressive, especially since the groups were unbalanced in age. Further manipulation by pooling two of the groups and then splitting by age on the basis of observed results invalidates any resulting P values. Indeed, as duration of stay is likely to be affected by so many extraneous factors, common sense suggests that this would be the least likely outcome to show an effect of suggestion. It is unfortunate that the most informative result—overall effect of treatments corrected for age — was not provided.

Bennett, Davis and Giannini (1985) stated that their "data...establish the phenomenon of a non-verbal response to intra-operative conversation"; that is to say, these patients could be persuaded later to touch an ear more frequently than the control patients. However, when the number of patients in each group who touched an ear at least once during interview are compared, using the correctly calculated and more appropriate *two-sided* Fisher's Exact Probability Test, $P = 0.08$. Furthermore, the tetrachoric correlation does not only seem inappropriate for such discrete data, but the correctly calculated value is 0.05 in place of the claimed $P < 0.001$. Finally, although there were more ear pulls per postoperative interview per patient in the suggestion group than in the control group (Mann–Whitney U test, $P > 0.02$), no preoperative record was made of the frequency of ear pulls in each group to show that they were initially similar in this respect.

Perhaps the most dramatic claim was made by Levinson (1965) some years ago, that four out of 10 subjects could, when later hypnotized, recall a simulated emergency enacted during deep ether anaesthesia. Unfortunately, there were no control subjects in this study, the hypnotist knew the nature of the "emergency" and insufficient details were published of the interview between the hypnotist and the subject to enable one to judge if leading questions were asked and to judge how accurately the subjects recalled the stimulus words. Despite allusions to further work, a more detailed study was never forthcoming.

It is our contention that these three papers, which might be considered to be key ones, do not provide adequate evidence. A more rigorous, critical review of methodology is called for when novel claims are made that have great theoretical or practical implications.

M. E. Wilson
Bath
D. Spiegelhalter
Cambridge

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Levinson, B. W. (1965). States of awareness during general anaesthesia. *Br. J. Anaesth.*, 37, 544

Sir,—We are very grateful to you for allowing us to reply to the letter by Drs Wilson and Spiegelhalter.

Unconscious perception during general anaesthesia is presently receiving more attention than ever before (Editorial, 1986), often in close connection with awareness (Jones and Konieczko, 1986). In designing our study (Bonke et al, 1986) we took all necessary precautions (randomization of applied procedures and double-blinding) to perform a valid investigation. Therefore, from a methodological point of view, our study has undoubtedly produced useful data for studying so-called unconscious perception during general anaesthesia.

We agree with Drs Wilson and Spiegelhalter that multiplication of the various P values would be sensible if all outcome variables were of equal interest and importance, and not strongly correlated. In our study, however, the outcome variables can be divided into five groups, three of which included highly correlated variables. Consequently, a multiplication factor of 14, as proposed by your correspondents, is exceedingly inappropriate and should be considerably lower. Therefore, the observed difference in postoperative stay between the three groups (table II) is certainly statistically significant, with a two-sided P value well below 0.05, instead of 0.056 as we are led to believe by Drs Wilson and Spiegelhalter. Moreover, for this main dependent variable a clear, documented hypothesis of effect was at hand (Pearson, 1961). Taking this into account, one must conclude that the observed difference is genuine and not explicable by chance alone.

The secondary analysis incorporating the explanatory contribution of age was performed because of the observed unbalance in age. This analysis clearly indicated that the observed beneficial effect of positive suggestion upon the duration of postoperative hospital stay only applies to older patients. An overall effect estimate of treatments on postoperative hospital stay, adjusted for age, was not provided because of the presence of interaction, meaning that the effects were different for different age groups. For that reason, providing an overall effect estimate adjusted for age, as Drs Wilson and Spiegelhalter proposed, had become meaningless. Of course, "final" evidence will, as usual, not be established until future studies have confirmed our findings

We would also like to add a few comments about the often cited study by Levinson (1965). In 1967, Levinson published a slightly more extensive report on his controversial study with hypnotizable, young patients. He reported that, apart from the four patients who recalled the pseudo-crisis almost verbatim, another four "displayed a severe degree of anxiety while reliving the operation ..., woke from hypnosis and refused to participate further." Not only are these reactions to hypnosis quite uncommon—certainly in such a high proportion of subjects—but it also seems inappropriate to ascribe these responses to "leading questions" or knowledge of the nature of the feigned crisis, by the hypnotist. Levinson's results may not have provided completely adequate evidence for so-called unconscious perception during general anaesthesia, but doing away with them by implying that his work can be ignored, is like throwing the baby out with the bathwater.

B. Bonke
P. I. M. Schmitz
F. Verhage
Rotterdam
A. Zwaveling
Leiden

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Pearson, R. E. (1961). Response to suggestions given under general anesthesia. *Am. J. Clin. Hypn.*, 4, 106.

Sir,—Bennett, Davis and Giannini (1985) described a study to examine non-verbal response to intraoperative conversation. While anaesthetized, 11 patients were presented with the tape-recorded suggestion that, in a postoperative interview, they would pull their ear to indicate that they had heard the intraoperative message. A control group of 22 patients was presented with operating room sounds. Subsequently, no patient had any conscious recall of intraoperative events, but the test patients were reported to be significantly more likely to touch their ear during the interview, and to spend longer total time in ear-pulling (experimental group made 66 ear-pulls for 667 s; control group made 18 ear-pulls for 98 s). While the authors claim that the data are evidence for a non-verbal response to intraoperative conversation (i.e. memory for events during anaesthesia), one should be guarded about the reliability of the results for the following reasons.

The primary difficulty concerns the methodology, where there is an omission of any pre-surgical assessment of "ear-pulling" in order to determine the baseline or natural frequency of the behaviour. Had such an assessment been made, one might then constrast the frequency of the behaviour before and after surgery. However, without such a baseline assessment one cannot determine unequivocally whether the post-surgical difference between the groups is the result of the intra-anaesthetic suggestion or of chance allocation to the experimental group of patients with a naturally higher frequency of the behaviour. With such small sample sizes and the biased allocation of patients to groups (2:1; control *v.* experimental), the latter probability is high.

The second major difficulty stems from the small size of the experimental group, where extreme reactions by one or two patients may give a misleading result. This is well illustrated by the measure of total time spent ear-pulling: two patients each spent 300 s pulling their ears, accounting between them for 600 s of the total 667 s spent by the 11 members of the group in ear-pulling. (Note that the 655 s total time cited by Bennett and co-workers in the text of the paper is incorrect both in the present Journal and in another report of the study published elsewhere (Bennett, Davis and Giannini, 1984); their table I provides data for each experimental patient and sums to 667 s). These same two patients also account for 29 of the 66 separate ear-pulls carried out by the experimental group. If the latter two patients were excluded from the analysis, it is unlikely that the experimental and control groups would differ significantly. The reader might make such an analysis for himself, but Bennett, Davis and Giannini (1985) provided raw data only for the experimental group.

The significance of the results is also thrown in doubt by the authors' use of a completely inappropriate statistical test of tetrachoric correlation between the variables of patient-grouping (experimental *v.* control) and the ear-touch response. That test is appropriate when *both* variables are continuous but, in the study concerned the variable of patient grouping is obviously discrete. The correct test to use in this case, where one variable is discrete and the other continuous, is the point biserial correlation. Again, the reader is unable to make such an analysis because the control group data are omitted from the report. One might also point out that a Fischer exact test carried out by the authors on the same data gave a value of $P = 0.05$. Clearly, by this measure, the difference the groups lies very much on the borderline between a significant treatment effect and chance alone.

Finally, the authors regard as significant the fact that an anaesthetized patient, within whose presence a surgeon made highly pessimistic comments concerning the quality of the bone graft being performed, took longer to recover and required more analgesics than other patients. The implicit conclusion is that exposure to the surgeon's comments had exerted a subconscious adverse influence upon recovery. However, given the surgeon's objective assessment of the unsatisfactory surgical procedure, it is surely more appropriate (and logical) to conclude that the patient's extended and painful recovery was a direct consequence of physical discomfort arising from imperfect surgery, rather than of subconscious trauma.

In conclusion, while one would not deny that there is evidence for subconscious registration of traumatic and neutral material during anaesthesia (for example Levinson (1965) and Millar and Watkinson (1983)), one would suggest that failings in the methodology, analysis and inference of the study by Bennett, Davis and Giannini (1985) render their results somewhat inconclusive.

K. Millar
Glasgow

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Millar, K., and Watkinson, N. (1983). Recognition of words presented during general anaesthesia. *Ergonomics*, **26**, 585.

Sir,—I respond first to the points made by Dr Millar concerning our research on assessment of intraoperative responses to operating room conversation (Bennett, Davis and Giannini, 1985).

Dr Millar asks that readers question the reliability of our results which indicated that patients can be instructed during operation on to carry out a behaviour after operation. Reliability is necessary to validity, and his is therefore a serious charge. In response, three answers are necessary: first, the study was our second. In the first (Bennett, Davis and Giannini, 1984) we believe we had established a reliable non-verbal indicator of intraoperative hearing and thus proceeded with several refinements to examine this specifically with the second study. Second, the response has been replicated by Goldman (1986) using chin touching. Third, we have a series of 48 patients that continue to show that the response can be elicited as long as highly motivating consent interviews are given to agreeable patients along with convincing and personally meaningful intraoperative appeals to engage in a consciously unmonitored behaviour after operation. Thus while healthy scepticism is warranted, my position on the topic must remain with what the data state.

In his critique, Millar suggests a "control count" of preoperative ear touching was necessary. While perhaps desirable, such a count is no more necessary than the degree of preoperative ear wax might be. By random assignment, behaviours, attributes, and differences among all extraneous variables are assumed to vary equally. There is no reason to expect *a priori* favouritism towards ear touching. Giannini, the third author of our original paper, for his doctoral dissertation, counted preoperative ear touching behaviour in his replication attempt. The behaviour was present to a minor degree and was equally spread over experimental and control groups. Preoperative ear touching did not affect the statistical analysis of the data. Our own more recent studies support this: preoperative behaviours are not a confounding factor in eliciting the response.

In the next paragraph, Millar wishes to exclude patients showing interesting data (large numbers of ear touching behaviours in the postoperative interview). Then the author wishes we had included raw data from the control group of 21 patients which describes ear touching during the postoperative interview. We had not anticipated such interest in our data and merely included summary frequencies for the control group at the bottom of figure 1 of the original article. The raw control group data are presented now (table I); it was our error not to include them originally.

After these promising results, we have since looked more closely at this response, a non-verbal response to an intraoperative message addressed to the patient, and found it to be robust (Bennett, Boyle and Willits, unpublished observations).

To Dr Millar's next point, we acknowledge the preference of one type of correlational analysis over another. Our use of a

TABLE I. *Data from experimental and control groups showing number of ear touches observed in postoperative interview and duration of total ear touches*

Experimental group			Control group		
Patient No.	No. ear touches	Duration (s)	Patient No.	No. ear touches	Duration (s)
1	1	15	12	0	0
2	2	2	13	0	0
3	1	1	14	3	11
4	17	300	15	0	0
5	9	25	16	2	4
6	0	0	17	0	0
7	0	0	18	1	1
8	6	6	19	0	0
9	14	14	20	2	2
10	4	4	21	0	0
11	12	300	22	0	0
			23	0	0
			24	0	0
			25	1	60
			26	4	12
			27	0	0
			28	0	0
			29	2	5
			30	2	2
			31	0	0
			32	1	1

tetrachoric analysis had to do with the assumption of the independent variables which could be considered continuous (Thorndike, 1978). Our "tetrachoric" correlation produces $r = 0.61$ while the "point biserial" correlation produces $r = 0.57$ and a significance (Fischer's exact test, one-tailed) of $P = 0.393$. The one-tailed test is appropriate as there is no reason to suspect that asking patients to do something should make them less likely to do it, while there is good reason to assume they will be more likely. The conclusion is that the data are statistically significant and meaningful.

Finally, Dr Millar, a psychologist, disagrees with the type of supporting case material we present. To this point our chief of anaesthesia as well as several well qualified anaesthetists and orthopaedic surgeons have not thought the claims from this case offensive. Recovery from surgery depends upon many factors and "insulting" intraoperative conversation may possibly be one of them. Indeed, both patients reported in the article were somewhat atypical because they had orthopaedic procedures on the lower extremities rather than the "hernia or cholecystectomy" of a series we had been running for some time and which totalled 55 patients: 22 hernia, 25 cholecystectomy, and eight orthopaedic.

Perhaps we should have presented, out of the 47 patients in the hernia/cholecystectomy group, the single patient who did have an anomalous recovery: a control cholecystectomy patient, she had by far the longest convalescence, partly as a result of myocardial infarction on the first day after operation day with no previous history. We conducted our standardized blind interview 8 days after operation. During the interview the patient broke off the hypnotic review of surgery quite early, in tears. She was clearly highly distressed at the approaching task of retrieving surgical memories, but was unable accurately to find a source for them, later stating that she was sad about her son's difficulty locating an apartment. This was the only intense crying behaviour of the entire series; as a precipitate, we have a recorded verbal event by the surgeon in clear language and no uncertain terms of the patient's weight, unattractiveness, and immediate unworthiness. These statements were made during closure of the peritoneum, coming some two-thirds of the way through the surgery. Finally, the importance of this surgeon to this patient was quite high. This case is reminiscent of Levinson's published series and of patients described in his thesis (Levinson, 1965, 1969). Similar affective and physiological responses to intraoperative meaningful messages are found in two more recent doctoral dissertations on the topic (Rath, 1982; Goldmann, 1986).

In summary, Dr Millar has correctly indicated the desirability of including control group raw data and of a statistical test which assumed a continuous distribution of values when dichotomous ones were more appropriate. He has erred, however, in his logic of insisting upon counting preoperative behaviours and he has erred in dismissing the discovery that the two patients with anomalously long recoveries from surgery (one discussed here and one in the original article) were, when we examined them, also the only patients exposed to particularly poignant insulting or pessimistic remarks by the surgical team. We were hoping to be polite about the sensitive topic of inappropriate intraoperative conversation, but these comments must be aired.

The previous letter, from Drs Wilson and Spiegelhalter, is of interest because it discusses three reports in the literature, including our own, and asks finally for "adequate evidence" of what patients learn and respond to during states of anaesthesia. Adequate evidence should, according to these authors, be in keeping with the "great theoretical or practical implications" of the data. They ask for science to inform us about this issue. Their request is the test of the scientific method: to follow where the data lead rather than where our assumptions lie. Yet the data that were presented in 1965 by the oft-quoted Levinson were not scientifically examined by these or other colleagues following up on this "novel claim" of fundamental importance for more than 20 years.

We disagree with these authors' criticisms of our data analysis, and refer them to Millar's commentary, while agreeing that the point biserial correlation is more appropriate than the tetrachoric correlation.

To be clear, our data may disturb some individuals who have held contrary assumptions. They are, however, valid and they point to further studies which will require closely monitored methods. The data are not definitive, nor are they meant to be. They are meant to establish two points: (1) that patients' retrospective verbal reports of amnesia are insufficient evidence that they did not learn something new for the period that they cannot recall. We are accustomed to pre- and post-anaesthetic discussions with patients that they do not later consciously remember, so that is not surprising; we also recognize that recognition memory is far better than spontaneous free recall; (2) what may be important is the finding that some patients may acquire a new response during operation and be consciously amnesic for it. Further work should look at anaesthetic variables, and this we have begun.

Patients have simply been assumed to be decerebrate when they haven't been able to recall the events of surgery. None of our 55 patients had recall, yet those instructed and asked to do so during anaesthesia responded and continue to respond. Similarly, Levinson's patients did not know anything consciously. Further work has recently been completed by L. Goldmann for a doctoral dissertation at Cambridge University. Working in collaboration with colleagues at Cardiff, Dr Goldmann reports that he was successful in establishing a postoperative non-verbal reponse (chin touching) by intraoperative requests to patients. He also reports observing affective sequelae to "insulting" surgical banter. Another recently published report (Stolzy, Couture and Edmonds, 1986) independently confirmed intraoperative verbal learning first reported by Millar and Watkinson (1983). In completely independent work, another doctoral dissertation (Rath, 1982) followed upon a series of studies and examined autonomic and physiological consequences of specific instructions given to adequately anaesthetized surgical patients. The results were convincing: patients received the instructions.

These studies have all shown convergence towards a model of the effects of intraoperative conversation during anaesthesia. This model uses other data from cognitive psychology on the early activation of knowlege structures before conscious registration which is ablated during adequate anaesthesia (Bennett, 1987). By use of grammatically meaningful phrases, linguistic expressions with high pertinence can automatically register and affect behaviour. Given the high motivation to survive and recover from anaesthesia and surgery, patients' nervous systems might be assumed to be attuned to pertinent events in the environment. One would hope these tentative conclusions can be refined by further experimentation.

H. L. BENNETT
Sacramento

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HAEMODYNAMIC DISTURBANCES DURING ANAESTHESIA IN A PATIENT RECEIVING VERAPAMIL

Sir,—The case report by Gorven, Cooper and Prys-Roberts (1986) documented the haemodynamic problems which may be experienced with patients receiving calcium channel blockers. Their case bears a number of similarities to the following one, and poses questions of management which must be faced by anaesthetists in similar circumstances.

A 65-yr-old, 109-kg Caucasian male was admitted for elective right cataract extraction and posterior chamber intraocular lens implant together with right excision of pterygium. He was known to have had an irregular heart rate for many years. He was usually active and able to shear sheep. He had no angina or symptoms of congestive cardiac failure. On admission his medication consisted of digoxin 250 µg in the morning and verapamil 80 mg each morning for control of his arrhythmia. Arterial pressure on these medications averaged 150/90 mm Hg during the day before operation. Before operation his ECG showed atrial fibrillation with controlled ventricular response and digitalis effect. On physical examination, heart rate was approximately 70 beat min^{-1} and there were minimal basal crepitations bilaterally. He was a big, overweight man, but denied dyspnoea on exertion. Chest x-ray showed a normal heart size and contours with a little overinflation of the lungs.

The patient received his normal medication before surgery and was premedicated with pethidine 100 mg and atropine 0.6 mg i.m. 1 h before surgery. On arrival in the anaesthetic room, the patient was calm. An ECG machine was attached (Lead II), a peripheral venous cannula was inserted and an infusion of Hartmann's solution commenced. After preoxygenation, anaesthesia was inducted with fentanyl 100 µg and thiopentone 375 mg. Tracheal intubation was facilitated by neuromuscular blockade with pancuronium 11 mg. Anaesthesia was maintained with 65% nitrous oxide in oxygen (C.I.G. monitor), delivered by a Campbell's ventilator through a circle system, supplemented with fentanyl 300 µg i.v. Systolic arterial pressure decreased from 166 to 120 mm Hg and heart rate increased from a pre-induction value of 64 beat min^{-1} to 163 beat min^{-1} after induction. Immediate concern prompted the writer to seek advice from a consultant physician, who recommended slow injection of verapamil 5 mg i.v. if the heart rate failed to settle. There was at this time a considerable pulse deficit.

It was decided to observe the situation closely, and systolic arterial pressure settled to between 100 and 110 mm Hg whilst the heart rate decreased slowly over 45 min to 90 beat min^{-1}. At the end of the procedure it was decided to administer naloxone 0.1 mg, but not to antagonize neuromuscular blockade, as the physician indicated atropine may have been responsible for the observed tachycardia. Soon after naloxone was given, heart rate increased temporarily to 183 beat min^{-1} as the patient was transferred to the recovery room. On admission the arterial pressure was 215/110 mm Hg and heart rate 124 beat min^{-1}. The patient awoke and was weaned from the Bennett ventilator within 10 min. Heart rate and arterial pressure decreased to close to preoperative values of 90 beat min^{-1} and 140/90 mm Hg. There were no further complications other than some multifocal ventricular ectopic beats which diminished during his stay in the recovery room.

The above report describes a patient presenting for anaesthesia and surgery while being treated with the calcium channel blocking agent verapamil and with digoxin for atrial fibrillation. He was not diagnosed as being hypertensive before surgery. Continuation of this therapy was unable to prevent rapid atrial fibrillation and a significant decrease in arterial pressure as a result of stressful stimuli in the perioperative period.

The writer has previously anaesthetized a number of patients receiving calcium channel blocking drugs, without incident. The excellent discussion of their case by Gorven, Cooper and Prys-Roberts (1986) with many similarities is relevant to the above report in which verapamil was the only calcium channel blocking agent exhibited. In this case further verapamil was not given, but the question remains, what therapy is appropriate when cardiac function is impaired under these circumstances?

G. B. H. Lewis
Armidale

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BOOK REVIEWS

F.F.A.R.C.S. Part 1 Practice Exams. By W. Aveling and S. Ingram. Published (Paperback) by Pastest Service, Hemel Hempstead. Pp. 176; indexed; illustrated. Price £8.50.

I was very interested to receive this book for review, it being a further publication in the successful Pastest series which has included books for the M.R.C.P., M.R.C.O.G. and many others. I believe this book to be a further step along the way of encouraging postgraduates to help themselves, and not rely on being spoon-fed.

This book contains two mock MCQ papers with answers, explanations and a method of self-assessment, three essay papers with outline answers, and 13 case histories with the relevant x-rays, ECG, graphs, etc. Further pages are devoted to commentaries, advice on the examination and lists of books.

This book is a very useful aid to any candidate preparing himself for the Part 1 F.F.A.R.C.S. (ENG.), but it needs to be read selectively to avoid losing the benefit of some of the sections. The candidate should obviously read the recommended book list and the advice about the nature of the examination right from the start. He would be better to defer attempting the various tests until his reading was well under way.

The advice given to the candidates on the nature of the examination and the strategies required is sensible, and I am particularly pleased to see the authors emphasizing the need for organization in learning. Disorganized, structureless learning must surely be one of the most potent factors in exam failure.

In the MCQ tests one can, of course, find points of disagreement over the interpretation, but this is common to virtually every other collection of MCQ. The candidate, if he finds he disagrees with the answer, should then be prompted to look at the original papers and discuss it with his colleagues. The candidate would, incidentally, be advised to write his MCQ answers on another piece of paper rather than marking the book, since this would allow him further attempts at the MCQ examination. In one sense it is a pity that there are only two sets of MCQ questions, since these can only really be used twice, after which there is a tendency for candidates to learn the answer patterns.

I was particularly pleased with the fact that the authors specifically direct the candidate to the correct page of the text book in their explanations, helping the candidate to rectify specific errors.

The model answers to the written questions are helpful, but the candidate should be aware that he can fail on the written paper, not because he doesn't know the information, but because he presents it badly. For that reason, while the model answers are a help with the content, the candidate should discuss his written answers with a senior colleague to make sure his presentation is acceptable.

The clinical material is an interesting and worthwhile section of the book and candidates, in commenting on the various case histories, again should do this in conjuction with a more senior colleague. It is very easy to imagine that what one does every day is practice common to all anaesthetists throughout the country, whereas it may just be what is done in that particular hospital under restricted circumstances.

This is a useful book which, when used properly, will be a valuable aid to ensuring success in the Part 1 Fellowship examination.

A. J. Asbury

Cardiopulmonary Bypass. Principles and Management. Edited by K. M. Taylor. Published by Chapman and Hall Medical, London. Pp. 439; indexed; illustrated. Price £37.50.

This is a multi-author text with 21 chapters covering the principles and management of cardiopulmonary bypass. The first five introductory chapters cover the history of perfusion, monitoring, anaesthesia for adults and children and surgical cannulation techniques. This section of the book is heavily biased towards current practice in Glasgow rather than providing discussion on a wider scale—the format used in the remaining chapters.

The middle portion of the book consists of nine chapters which discuss the adequacy and consequences of pulsatile and non-pulsatile perfusion, plus the principles of oxygenation and specific aspects of bubble and membrane oxygenation. There is also a chapter on counter-pulsation techniques. The final section of the book covers a variety of topics including anticoagulation, blood trauma and conservation, microemboli, myocardial protection and safety during cardiopulmonary bypass.

There are particularly authoritative chapters discussing pulsatile perfusion by Professor Taylor (the Editor), bubble oxygenation by Bethune, microemboli by Pearson and myocardial protection by Braimbridge. I also enjoyed the early, rather didactic chapters on anaesthesia for cardiac surgery, and the discussion on priming fluids by Tobias.

This volume suffers the inevitable deficiencies of a multi-author text. There is some overlap from chapter to chapter and, although well referenced, few of the references quoted are after 1984. Cerebral function and cerebral function monitoring are discussed briefly in many chapters, but such important topics surely warrant a separate chapter written by a current expert in the field. Similarly, there is little information on complement changes and the immune response during cardiopulmonary bypass. Several authors over-emphasize the historical aspects of the subject under discussion and, in particular, the chapter on counter-pulsation techniques describes many outdated methods of circulatory assist, but does not discuss the use of current ventricular assist devices or artificial hearts.

The above criticisms are relatively minor and this very worthwhile book brings together, in one volume, a description and discussion of the major topics relating to cardiopulmonary bypass. It is certainly a book which all cardiac anaesthetic and surgical departments should have in their library, and even at the price of £37.50, many individuals would find this text a worthwhile expense.

John W. W. Gothard

Essential Anaesthesia, 1st Edn. By F. R. Ellis and I. T. Campbell. Published by Blackwell Scientific Publications. Pp. 130; indexed. Price £6.95.

This interesting little book contains 24 short chapters in 120 pages and costs £6.95. Unusually, the reader is not told where each author works, nor the Hospital or University appointments he holds. The book is without illustrations, but it presents a brief and easily understood account of many topics related to anaesthesia and is intended for medical and nursing students, especially those attending an anaesthetic attachment.

Like Punch's curate's egg, it is good in parts, and there are some excellent chapters, notably those on Preoperative Assessment and Intercurrent Disease, both of which should be read by all surgical residents. There are very good chapters on Principles of Anaesthesia, Monitoring, Local Anaesthesia, Intractable Pain, and on anaesthesia for many of the specialties, such as Paediatrics, Dentals and Obstetrics.

Some chapters, however, seem rather aimless, because the authors have attempted to provide *some* information on every conceivable heading, with the result that much of the content is too superficial, and the need to omit complex detail sometimes results in misleading inaccuracies. Inevitably, there could be some improvements. The statement "Repeat halothane anaesthetics within a six-week interval should perhaps be discouraged" is much too weak to fit our current obsession to avoid such a situation at all costs. The statement in the paragraph on night sedatives, "The most useful drugs are found to include chloral hydrate, nitrazepam, barbiturates and some phenothiazines", seems an inappropriate way to introduce this subject to students, when benzodiazepines (including nitrazepam) must account for the vast majority of currently-prescribed night sedatives and, in the reviewer's experience, the others are seldom indicated nowadays.

In the chapter on Care of the Unconscious, the signs of airway obstruction are detailed. A golden opportunity has been missed by omitting the most important sign of all—the *absence* of gas coming out of the mouth with each attempted breath, despite the obvious chest and abdominal movements in the obstructed patient.

The authors have been unfortunate in preparing this book during a time when there has been a decline in popularity or a withdrawal of several agents, and the emergence of so many others. There is, therefore, an imbalance in the importance given to some drugs in the text. Enflurane, which is probably becoming the most used inhalation agent, is given only three lines, and isoflurane is not mentioned.

All of these preceding comments are, however, only minor criticisms of a useful book, which provides an enormous amount of helpful and important information as well as many eye-openers for the uninformed student wishing to learn about anaesthesia and its many related topics.

A. G. Macdonald

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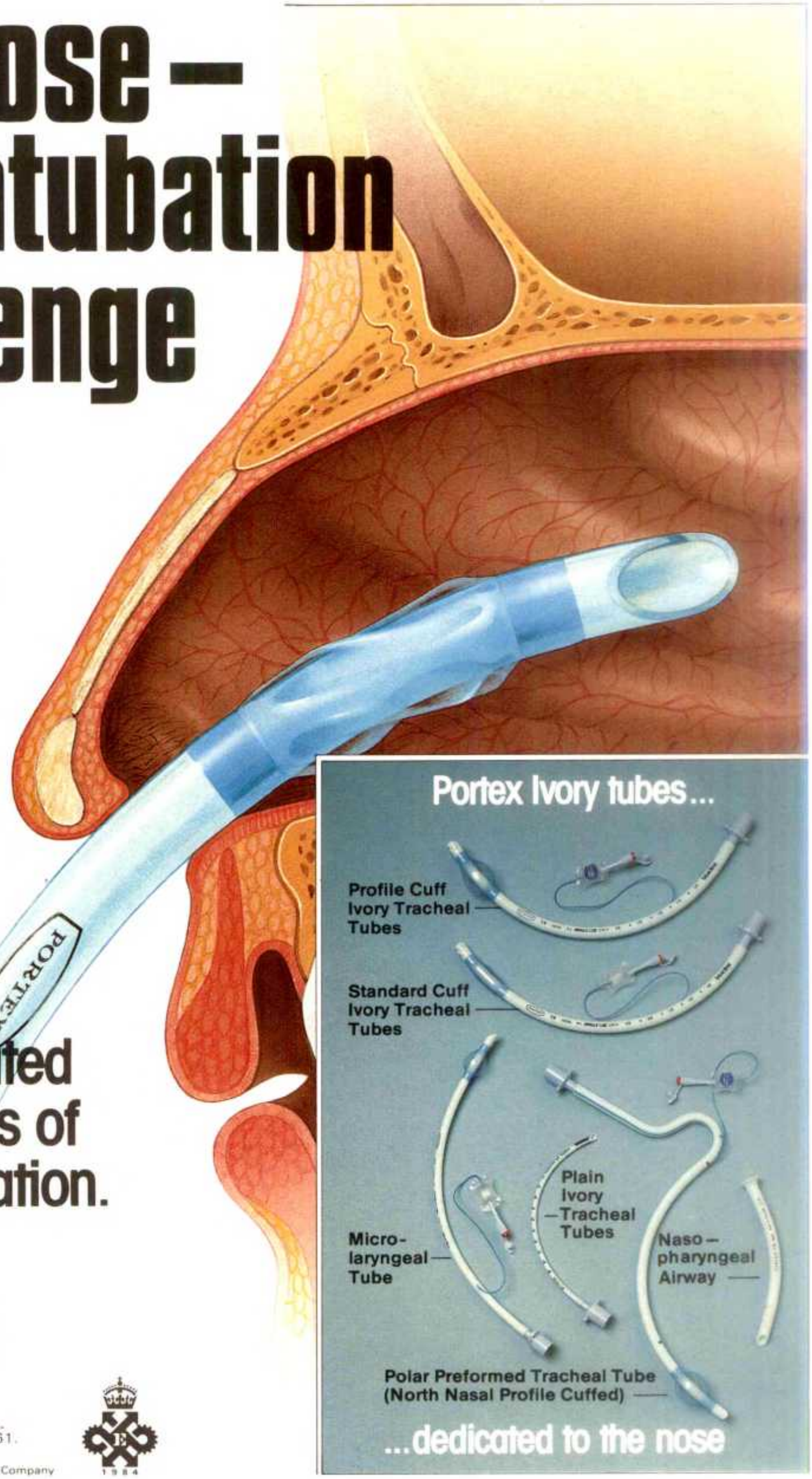
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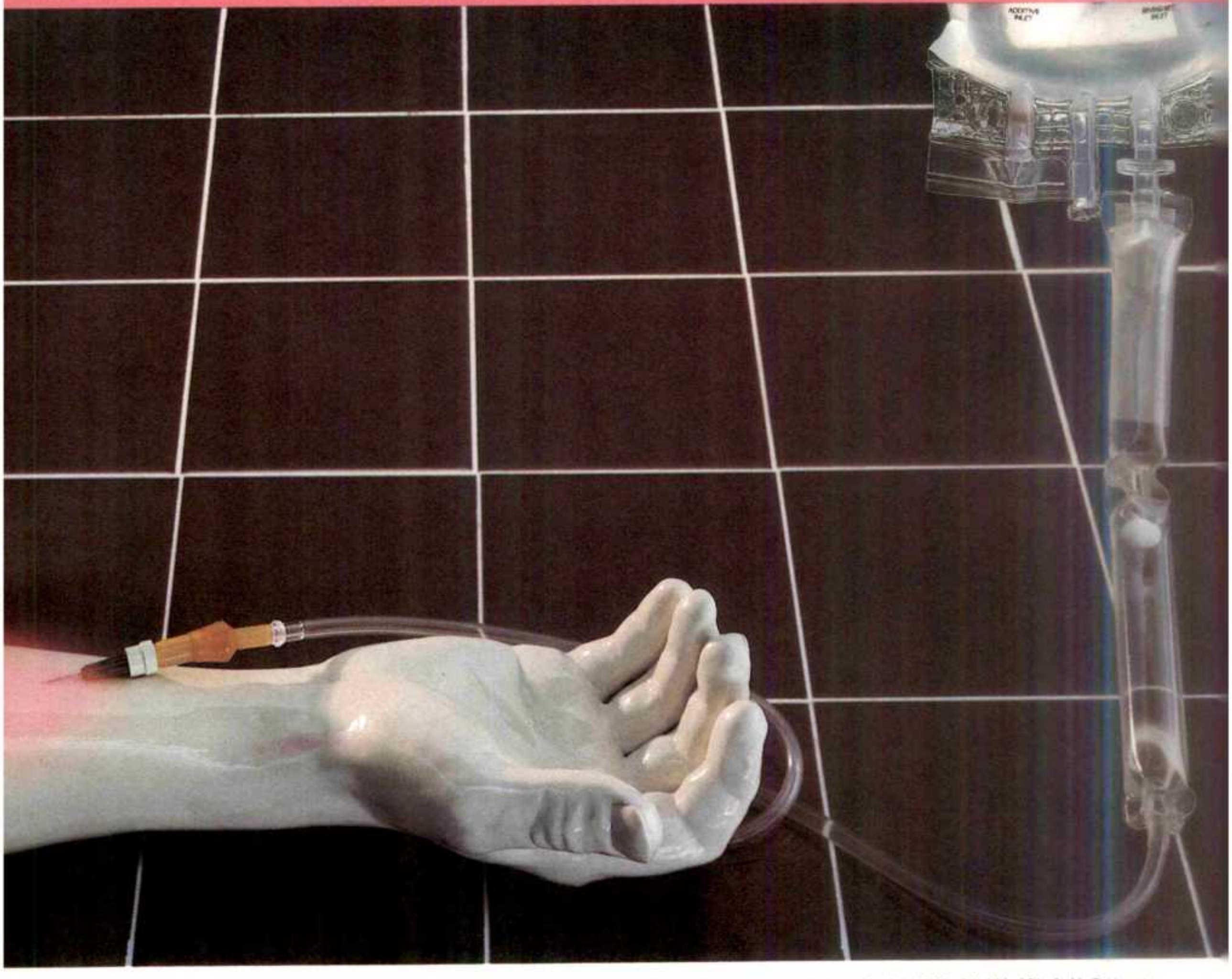

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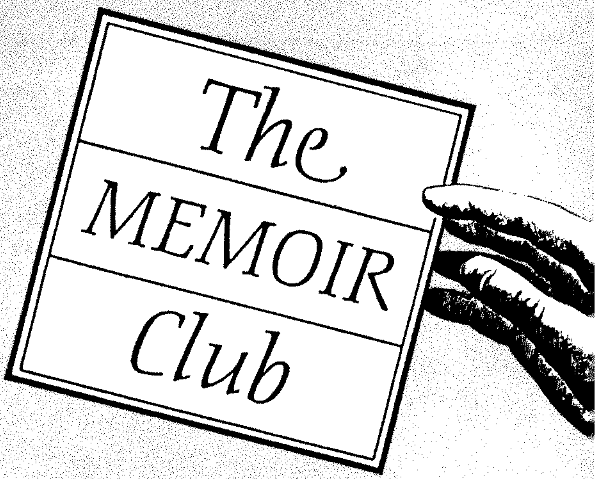

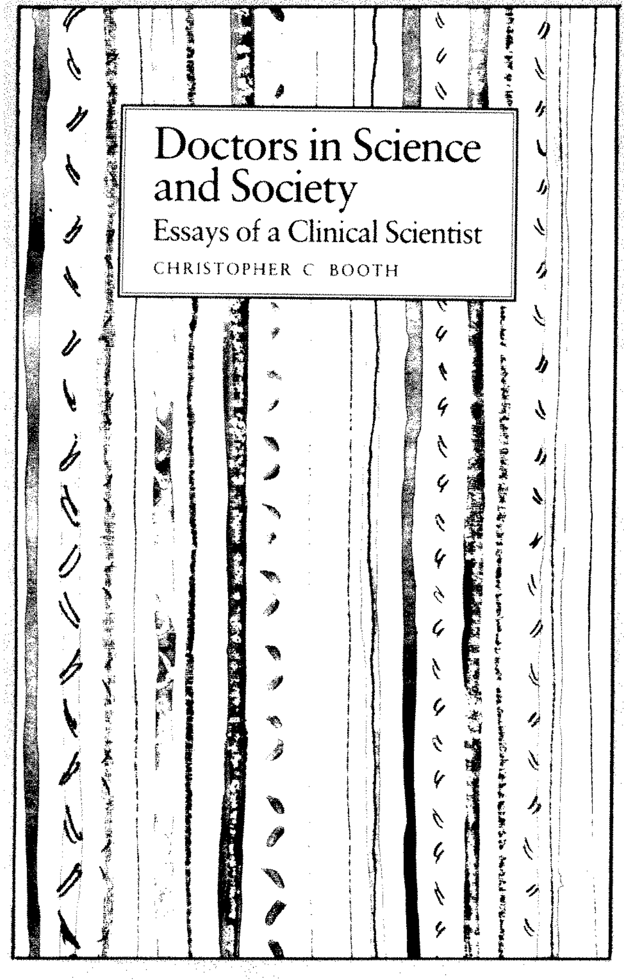

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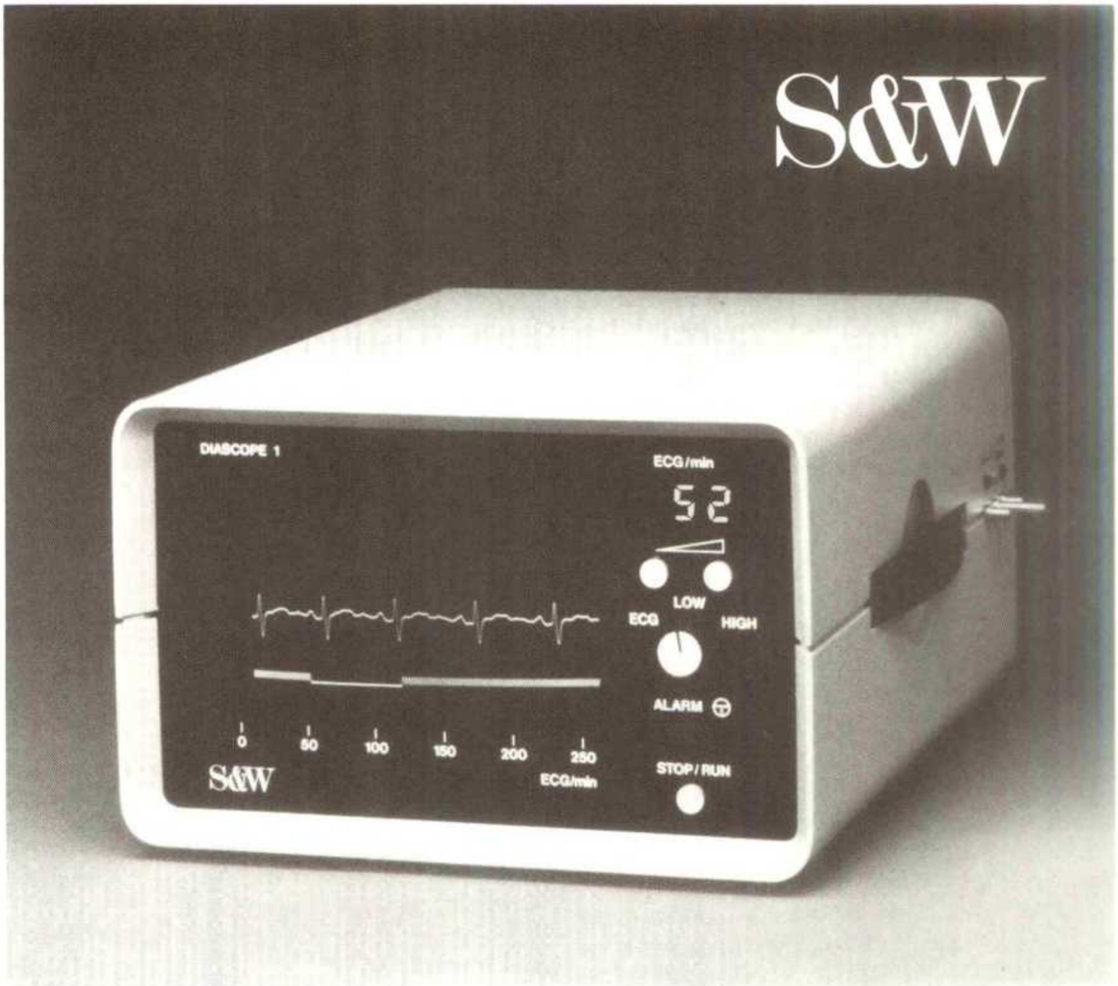

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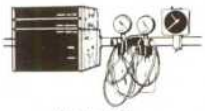

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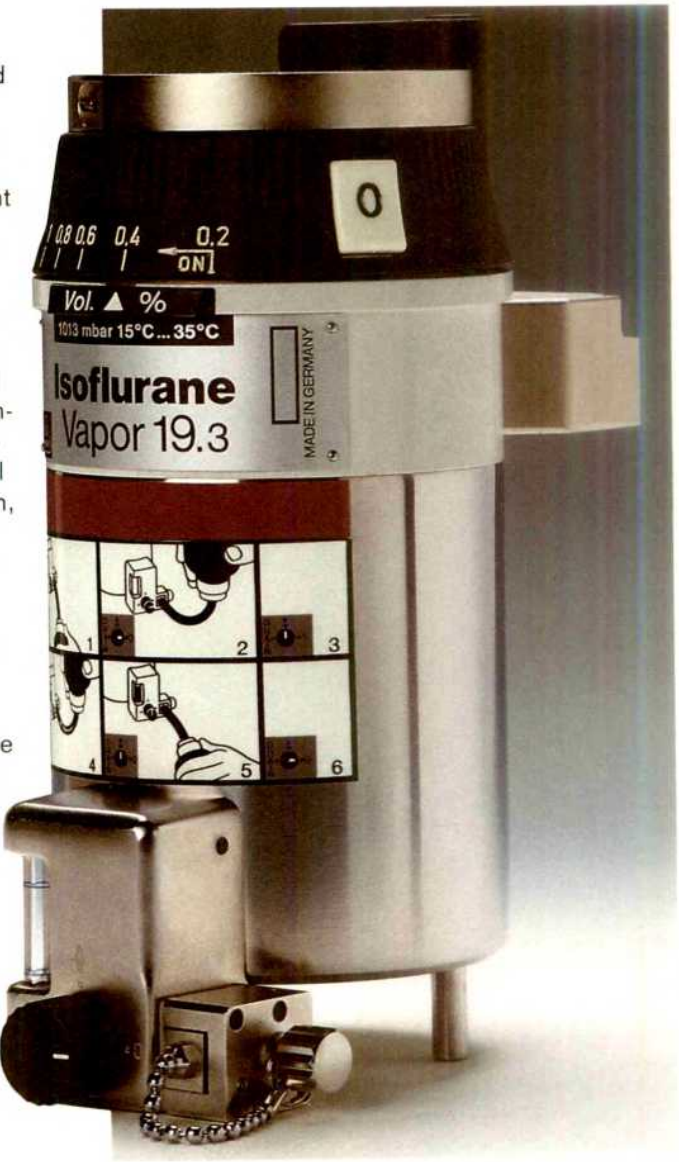

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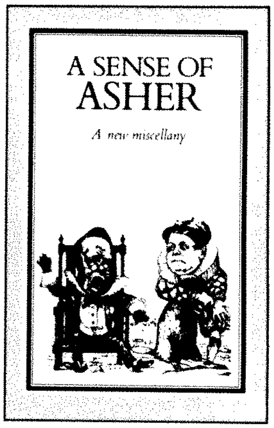

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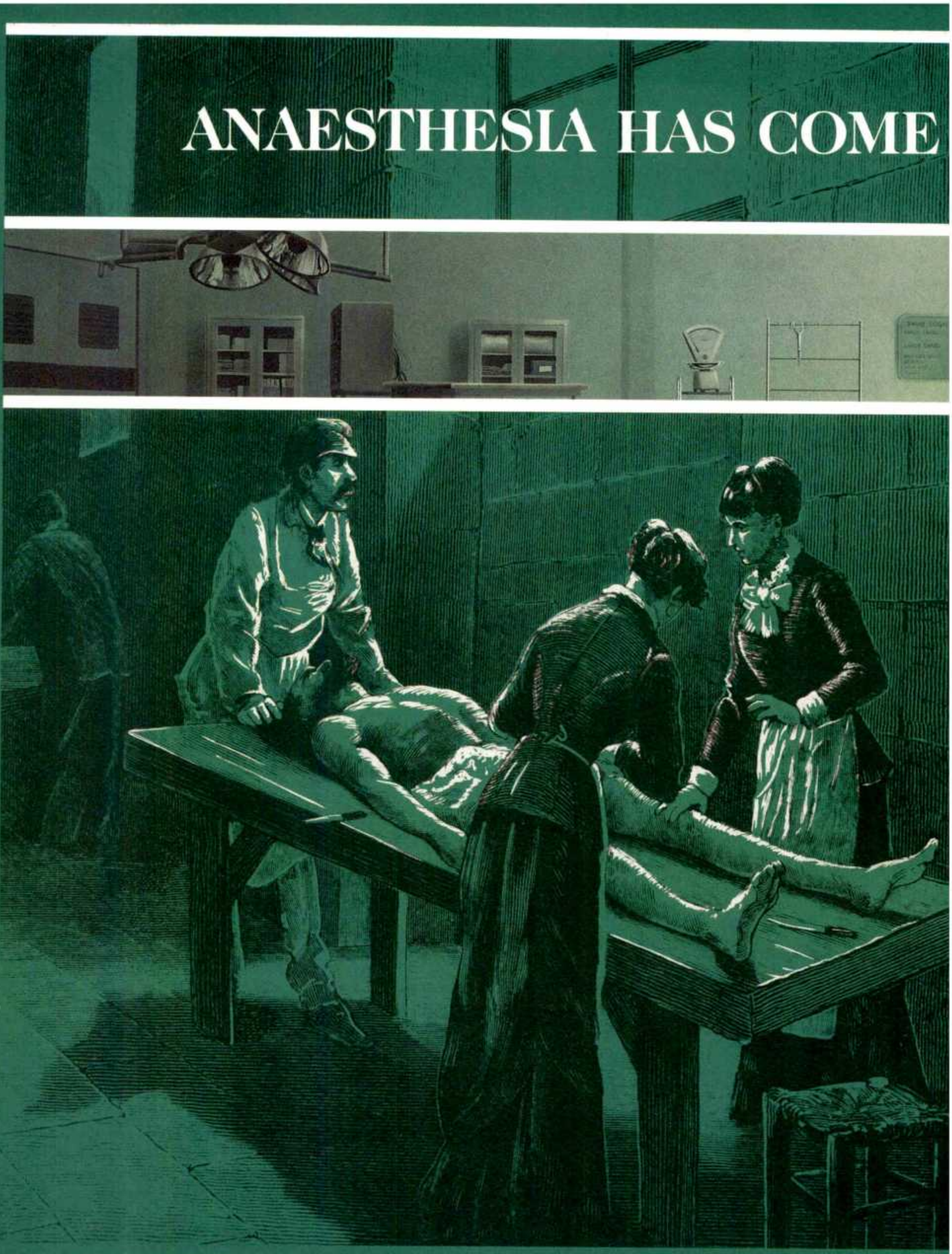

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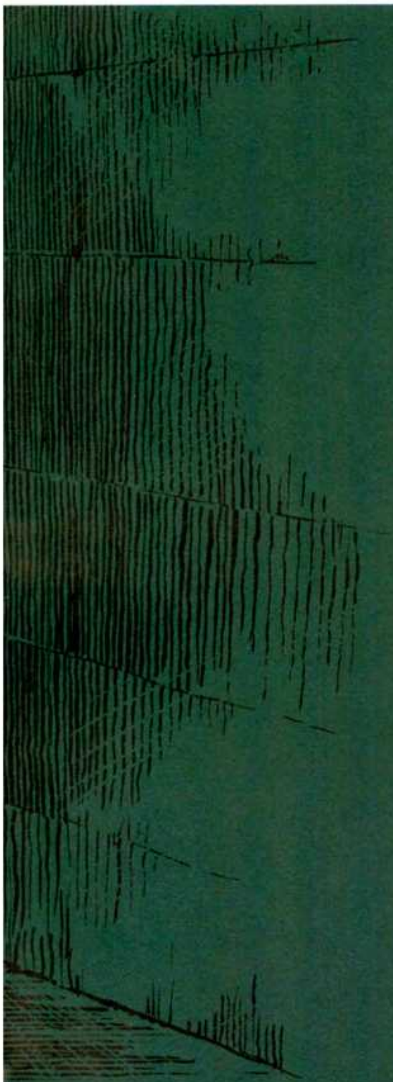

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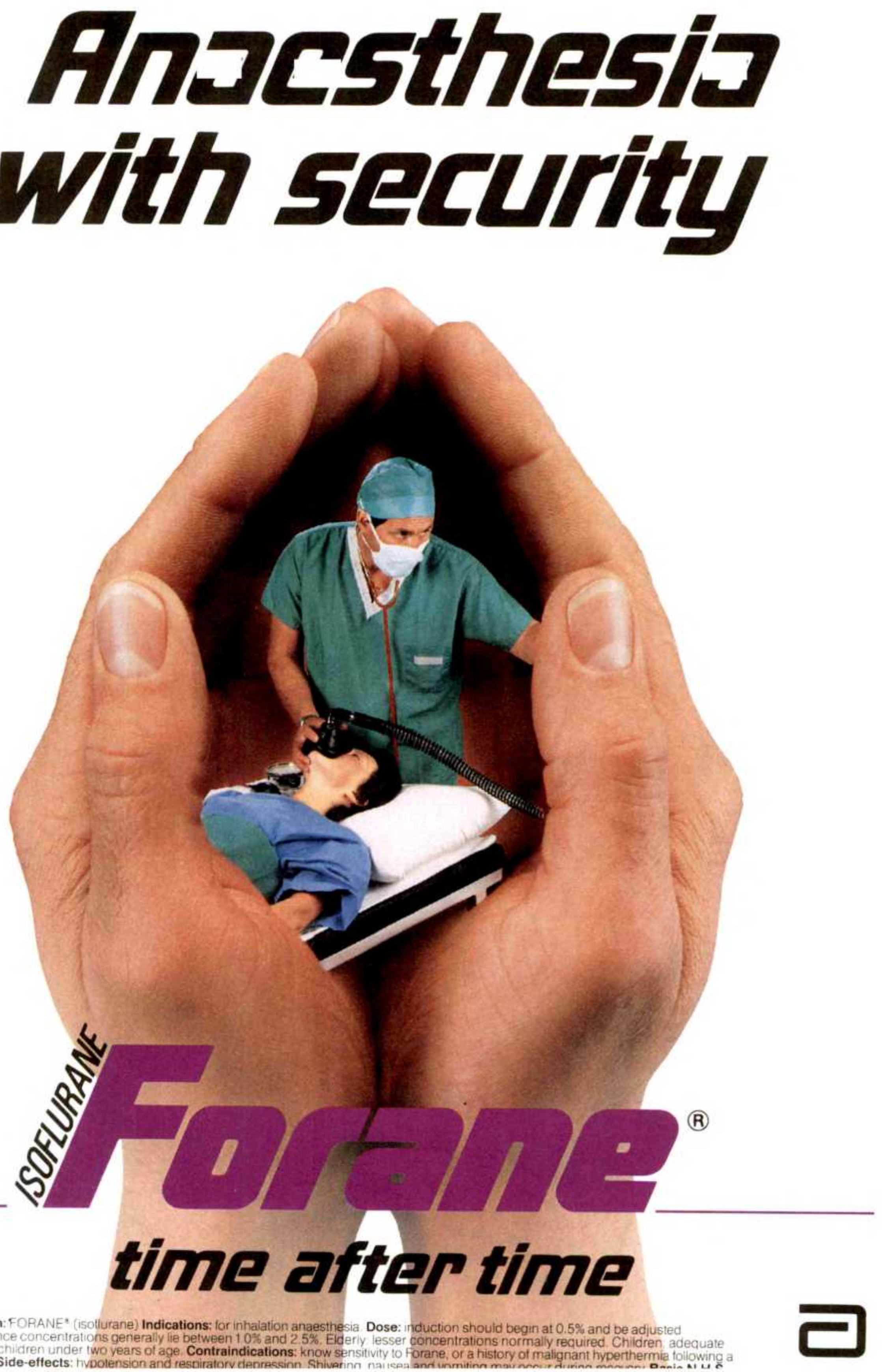

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BRITISH JOURNAL OF ANAESTHESIA

VOLUME 59, No. 11 NOVEMBER 1987

EDITORIAL

ANAESTHESIA: A PRACTICAL OR IMPRACTICAL CONSTRUCT?

The concept of anaesthetic "depth" is ingrained in every anaesthetic trainee from the outset of training. Yet this concept is illusory, and the continuing search for some method to measure anaesthetic depth (Robson, 1969; Saunders, 1981) resembles that for the Philosopher's Stone. In this issue, Evans, Bithell and Vlachonikolis investigate the relationship between spontaneous and evoked oesophageal motility in man, and the end-expired concentration of halothane. Is this a new phenomenon, or is it MAC (minimum alveolar concentration) in disguise?

A series of correspondence in *Anesthesia and Analgesia* has yet again focused attention on our inability to define the phenomenon which we use daily to render patients insensitive to the trauma of surgery (Russell, 1985; Pinsker, 1986; Kissin and Gelman, 1987). The term *anaesthesia*, introduced by Oliver Wendell Holmes in 1846, was apposite: it was an attempt to describe a new phenomenon in a single word. While that word has precisely the same meaning to many of us today—that is, the state in which a patient is insensible to the trauma of surgery—it is used more liberally and also more loosely than before. Pinsker (1986) rightly questions our definition of anaesthesia, but compares the term with that of *sickness* which, like *shock*, is too non-specific to be of value in present day medical practice. Perhaps the reason why the term anaesthesia is so difficult to define is that successive generations of practitioners of the art have centred their concepts around the effects of the drugs available to them, rather than the responses of the patient to the trauma of surgery, and the suppression of those responses by the wide variety of drugs now available. In the mid-nineteenth century only nitrous oxide, di-ethyl ether and chloroform were available to induce the state of general anaesthesia.

In order to clarify our definitive understanding of anaesthesia, I offer first some definitions of essential terms, as a prelude to an alternative concept that surgery, as an example of noxious stimulation, induces a variety of reflex responses, each of which may be modified independently to the benefit of the patient.

Let us start with an essential premise, that *pain is the conscious perception of a noxious stimulus*. In this context, the state of anaesthesia can be defined as that in which, as a result of drug-induced unconsciousness, the patient neither perceives nor recalls noxious stimulation. Such a definition is entirely consistent with Holmes's original concept of anaesthesia, and is also consistent with most of our present use of the word. However, in that loss of consciousness is a threshold event, it follows that anaesthesia is an all-or-none phenomenon. There cannot be degrees of anaesthesia, nor for that matter can there be variable *depths* of anaesthesia. All other attributes of anaesthetics, the drugs which produce the state of anaesthesia, can be classed as alternative pharmacological properties of the drugs, and not as components of the state of anaesthesia. In many respects the term *hypnosis* is synonymous with anaesthesia as it implies a drug-induced sleep. Confusion has arisen unnecessarily because hypnosis (mental block) was proposed as a component of anaesthesia (Woodbridge, 1957), together with analgesia (sensory block), muscle relaxation (motor block), and suppression of reflexes. Pinsker questions our inability to distinguish between hypnosis and amnesia as components of anaesthesia, implying that recall indicates a failure to anaesthetize (Eich, Reeves and Katz, 1985). This is admittedly a philosophical problem, in that patients who were apparently in a state of anaesthesia have been made to recall under the influence of hypnotism (Levinson, 1965; Cherkin and Harroun, 1971).

Analgesia is normally defined as diminished or abolished perception of pain in an otherwise conscious patient. Thus we classify mild (aspirin) or powerful (opioid) analgesics according to their propensity to modify the perception of pain without significantly modifying the patient's consciousness. Given in sufficient dosage, opioids can produce a state indistinguishable clinically from that induced by i.v. or inhalation anaesthetics.

Unlike the latter, opioid-induced anaesthesia can be achieved only by doses which cause total suppression of ventilatory drive. There is no need to confuse this pharmacological effect of opioids with their specific analgesic or ventilatory depressant properties mediated at specific opioid receptors. There is little evidence at present to link the "anaesthetic" state induced by large doses of opioids to receptor-mediated activity (Dodson and Miller, 1985).

Muscle relaxation. Before the advent of drugs which induce neuromuscular blockade, adequate muscle relaxation for surgical access to the abdominal cavity could be achieved by increasing the inhaled concentration of volatile anaesthetics. It was, therefore, not unreasonable at that time to regard this dose-dependent pharmacological effect of the drugs which produced anaesthesia as a component of the state of anaesthesia. However, it is illogical and confusing to include muscle relaxation induced by neuromuscular blocking drugs as a component of the state of anaesthesia (Woodbridge, 1957; Kissin and Gelman, 1987). Muscle relaxation, however achieved, is a desirable goal to satisfy the requirements of the anaesthetist for laryngoscopy and the surgeon for surgical access, but it is neither a component of anaesthesia, nor an alternative to inadequate anaesthesia. The misery caused to many patients who have been aware during supposed general anaesthesia could have been avoided if this confusion had never arisen.

Responses to Noxious Stimulation

An alternative approach to understanding the effects of drugs which produce anaesthesia, analgesia or muscle relaxation, is to consider the way in which animals (including humans) respond to noxious stimulation. A noxious stimulus is one which can cause potential or actual damage to cells, and may be produced by mechanical (surgical injury), chemical, thermal or radiation injury. Surgery sets up a continuous noxious stimulation, of varying degree and character, during and for a variable period after an operation. Whatever the nature of the noxious stimuli, they generate action potentials which are transmitted by Aδ and C fibres in spinal or cranial sensory nerves. These action potentials may be relayed centrally or may set up reflex responses at a spinal level, particularly when the stimulus arises from visceral rather than somatic origins (Cervero, 1985). In addition to evoking the perception of pain (in a conscious subject), noxious stimulation also evokes a number of somatic and autonomic reflexes which Sherrington termed "pseudaffective" reflexes. These reflexes occur simultaneously with the perception of unpleasant sensory experiences (Jänig, 1985; Schmidt, 1985), and are particularly prominent when evoked by stimulation of abdominal or thoracic viscera. The continuation of noxious stimulation into the post-operative period also evokes a metabolic and endocrine response (Kehlet, 1982).

Figure 1 shows a scheme of such reflex responses to noxious stimulation, ranked from left to right in the order in which they are suppressed by general anaesthetics.

Sensory

Impulses of somatic origin are relayed through thalamic nuclei and projected to the sensory cortex where there is spatial representation of the anatomical distribution of the stimulus. Good resolution of spatial localization is a feature of somatic sensory input, in contrast to the poor

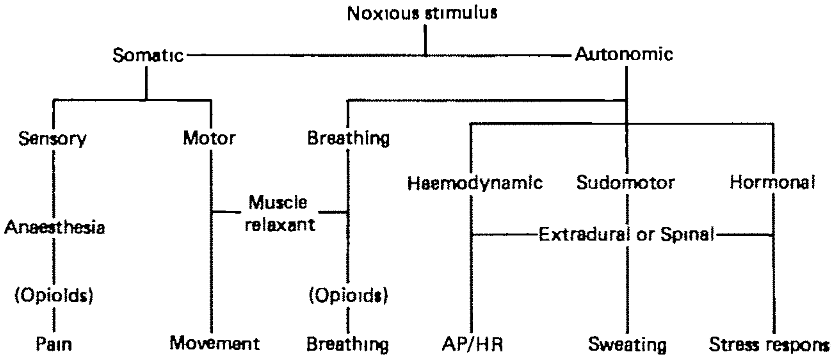

FIG. 1. Suppression of responses to noxious stimuli.

localization characteristic of visceral stimulation (Cervero, 1985) which does not have spatial representation in the cortex. Perception of pain, either of somatic or visceral origin, is dependent on the state of consciousness, and may be of the "fast" or "slow" modality according to the transmission by Aδ or C fibres, respectively.

Suppression of both perception and recall of pain can be achieved with blood concentrations of either i.v. or inhalation anaesthetics which are too low to suppress the motor responses.

Motor

The motor response to somatic noxious stimulation is characterized by reflex withdrawal of the stimulated part. Suppression of this simple reflex has been used as the basis of the main quantitative indices of anaesthetic potency, the minimum alveolar concentration (MAC) for inhalation agents (Merkel and Eger, 1963; Eger, Saidman and Brandstater, 1965), or the minimum infusion rate (MIR) for i.v. anaesthetics (Prys-Roberts and Sear, 1984). In the normal way that these indices are determined in man, approximately 50% of the patients will move in response to the initial surgical incision; yet none of the patients who moved, in a series of the author's studies of i.v. anaesthetics, recalled any part of the period of anaesthesia and the associated surgery. It is therefore implicit, that the blood concentration of anaesthetic required to suppress the somatic motor response is higher than that required to induced unconsciousness, and by implication, perception of pain.

Breathing

Under conditions of clinically acceptable anaesthesia with inhalation or i.v. agents, increased frequency and volume of ventilation, breath-holding or laryngospasm can occur, even though there is no somatic motor response to the surgical stimulus. Greater concentrations of anaesthetics are required to suppress breathing responses to somatic noxious stimulation, than to suppress motor responses or to produce unconsciousness.

Autonomic responses

Noxious stimuli cause reflex activation of the sympathetic nervous system, which can be considered a part of the "Abwehrverhalten" (General Defence Reaction) as observed in animals (Hess and Brugger, 1943; Hess, 1949; Hilton, 1982). During clinical anaesthesia the manifestations of these responses may be modified by the use of drugs which specifically block central or peripheral transmission of sympathetic nervous action potentials (e.g. clonidine, or β-adrenoceptor antagonists). The autonomic responses can be classified simply into sudomotor, haemodynamic and hormonal.

Sudomotor responses (sweating) are commonly observed during nitrous oxide in oxygen–muscle relaxant–opioid anaesthetic combinations, mainly in response to visceral (intra-abdominal or intra-thoracic) manipulations. They are readily suppressed by low concentrations of volatile or i.v. anaesthetic supplements (Jänig and Räth, 1980).

Haemodynamic responses represent the effects of increased sympatho–adrenal activity on the cardiovascular system. The most obvious effects are increased arterial pressure and heart rate, the two variables most commonly monitored in routine anaesthesia. These responses occur commonly in response to both anaesthetic (laryngoscopy) and surgical stimuli, even when anaesthetic concentrations are high enough to prevent sensory, motor and breathing responses. Roizen, Horrigan and Frazer (1981) introduced the concept of MAC-BAR as a correlate of MAC, being the alveolar concentration of an anaesthetic which would suppress haemodynamic and adrenergic responses in 50% of patients. They found that the ratio of MAC-BAR to MAC was 1.45 for halothane and 1.60 for enflurane. Ausems and colleagues (1986) determined the plasma alfentanil concentration (Cp_{50}) at which the haemodynamic, autonomic and somatic responses to surgery were suppressed in 50% of patients. Both these studies are consistent with the concept of a ranked order of reflex responses to noxious stimulation, in which the sensory class of response was abolished at the lowest concentration of anaesthetic or analgesic drug.

Hormonal responses to the injury of surgery have been long recognized because they can be measured well into the postoperative period. They are difficult to suppress by volatile anaesthetics, but can be partially suppressed by high doses of opioids (Hall et al., 1978) and by regional blockade (Kehlet, 1982). They are only partially suppressed by beta-adrenoceptor blockade (Cooper et al., 1980).

A Restatement of Concepts

Analgesia, muscle relaxation and suppression of autonomic activity, are all discrete pharmacological effects which can be achieved independently by specific drugs. While a number of inhalation and i.v. anaesthetics, and opioid analgesics, may exert some or all of these effects to a greater or lesser degree, the suppression of sensory perception is the only feature common to all general anaesthetic agents. If one accepts the premise that the ranked order of responses to noxious stimulation is a valid representation of the events associated with surgery, then it is logical to consider anaesthesia as that state which ensures the suppression of the somatic and visceral sensory components, and thus the perception of pain.

Analgesia, muscle relaxation, and suppression of autonomic activity, are not *components* of anaesthesia. Rather they should be considered as desirable supplements to the state of anaesthesia as a means to enable surgery to be performed. The use of low concentrations of anaesthetics with muscle relaxants has resulted in an unacceptably large number of patients being aware during general anaesthesia. Any reliable indicator that the level of anaesthesia is adequate to ensure lack of awareness in the presence of muscle relaxants, is therefore highly desirable.

Returning to the question posed earlier about the phenomenon of oesophageal motility and its correlation with anaesthetic "depth", one must conclude that this is a visceral (autonomic) motor function, in that spontaneous and evoked oesophageal contractions are more akin to visceral peristalsis than to somatic muscular activity. However, the graded suppression of oesophageal movements and their correlation with end-tidal halothane concentrations is hardly surprising; it can be considered to be a visceral MAC. A similar relationship has been observed during infusions of propofol (I. Norley and C. Prys-Roberts, unpublished observations).

Other methods have been described to achieve the same end-point, although they have involved different modalities such as the EEG and its derived parameters (Rampil et al., 1980; Schwilden, Schüttler and Stoeckel, 1985) and brain stem auditory evoked responses (Robson, 1969; Thornton et al., 1984). These clearly demonstrate a dose–effect relationship for many anaesthetic agents, but do not answer that fundamental question: is it feasible to find some measure which will *ensure* that the patient will be unaware of, and will not recall, events and sensations during surgery? The findings of Evans and his colleagues show that oesophageal motility, as a non-invasive monitor of visceral motor suppression, can be useful. While the presence of oesophageal activity, either spontaneous or evoked, may imply anaesthesia inadequate to prevent awareness, we cannot, in the present state of knowledge, be certain that absence of oesophageal motility *guarantees* that the patient is adequately anaesthetized!

Cedric Prys-Roberts

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RELATIONSHIP BETWEEN LOWER OESOPHAGEAL CONTRACTILITY, CLINICAL SIGNS AND HALOTHANE CONCENTRATION DURING GENERAL ANAESTHESIA AND SURGERY IN MAN

J. M. EVANS, J. F. BITHELL AND I. G. VLACHONIKOLIS

SUMMARY

The effects of a range of concentrations of halothane upon lower oesophageal contractility (LOC) and on defined clinical signs has been studied in patients undergoing surgery. Changes in clinical signs were assigned a numerical value by means of a scoring system. One hundred and eighty-one sets of measurements were made in 46 patients exposed to concentrations of halothane between 2.0 and 0.5 minimum alveolar concentration (MAC). The results were examined to identify relationships between (i) the clinical signs and alveolar halothane concentration, (ii) the clinical signs and LOC and (iii) the changes in LOC and alveolar concentration; significant correlations were found between these variables. Decreasing alveolar halothane concentration was associated with an increase in LOC and these increases in LOC were also associated with increases in the clinical score.

Changes in lower oesophageal contractility (LOC) have been described during general anaesthesia in man. An increase in LOC is seen as anaesthetic dose is decreased (Evans, Davies and Wise, 1984).

The human oesophagus is unusual in that the muscles in its lower half are non-striated gut muscle not susceptible to paralysis by skeletal neuromuscular blocking agents. Thus the lower oesophagus retains its potential activity despite full skeletal muscle paralysis. The oesophageal musculature of most animals is predominantly skeletal; in some primates and the American opossum the anatomy of the oesophagus is similar to that in man.

Measurements of LOC provide two prime derivatives. Spontaneous lower oesophageal contractions (SLOC) are non-propulsive contractions which appear with increasing frequency as the dose of anaesthetic is reduced. The origin of non-propulsive contractions is not intrinsic to the oesophagus, but lies in the vagal motor nuclei and adjacent reticular activating system in the brain stem and is mediated by efferent vagal pathways. Provoked lower oesophageal contractions (PLOC) are obtained by the brief inflation of a small balloon in the lower oesophagus. This stimulus may provoke a secondary peristaltic response which, typically, increases in amplitude as anaesthetic dose is decreased. A recording of LOC is shown in figure 1.

An investigation was undertaken to examine the effect of a range of doses of halothane upon LOC, and to attempt to provide some additional correlation with a measure of clinical signs. In order to represent the effect of halothane upon clinical signs, a scoring system was used (Evans and Davies, 1984). The scoring system was based on measurable variables such as arterial pressure and heart rate, as well as sweating and lachrymation, since these were considered to be as significant as the cardiovascular variables. The scoring system had the additional function of providing a standardized means of limiting the decrease in halothane concentration supplied to the patient so as to protect the patient from the risk of awareness during the investigation.

JOHN M. EVANS, M.B., B.CH., F.F.A.R.C.S., Nuffield Department of Anaesthetics, Radcliffe Infirmary, Oxford. JOHN F. BITHELL, D. PHIL.; IOANNIS G. VLACHONIKOLIS, D. PHIL.; Department of Biomathematics, University of Oxford, Oxford.
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Correspondence to J.M.E.

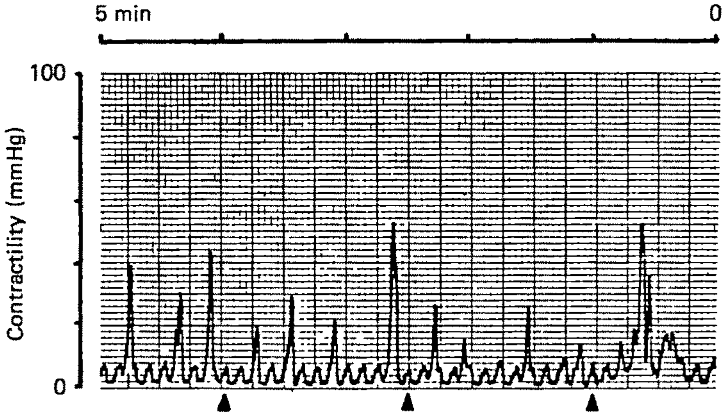

FIG. 1. A recording of lower oesophageal contractility from an anaesthetized, paralysed, ventilated patient. There is a regular low pressure signal arising from transmitted positive pressure ventilation. The markers indicate provocation by balloon distention and a variable provoked response is seen to follow. Additionally, there is much spontaneous activity between provocations.

It was decided to study a single volatile inhalation agent, halothane, for which a substantial clinical and experimental data base was available. Our experience suggests that halothane is typical and other inhalation and i.v. anaesthetics will have a grossly similar equipotent effect upon LOC.

PATIENTS AND METHODS

Patients

Adult patients undergoing elective abdominal, pelvic or lower limb surgery were studied. The investigation was approved by the local Ethics and Research Committee and consent was obtained after a verbal and written explanation of the investigation had been provided. Patients were in good general health, were not receiving any current medication and were free of symptoms or evidence of oesophageal disease. Specific records were made of patients' age, weight, height, alcohol consumption and tobacco consumption.

Anaesthesia

Patients were interviewed the day before surgery and offered premedication (lorazepam 0.05 mg/kg of body weight by mouth, 1–2 h before operation). It was explained to the patients that premedication would ideally be omitted from the investigation, but they would be free to receive it if they preferred.

Anaesthesia was induced with etomidate 0.3 ml kg^{-1} (accompanied by pancuronium 0.1 mg kg^{-1}). The lungs were inflated with oxygen and halothane at an initial inspired concentration *corresponding* to an end-expired concentration of 3.0 MAC; this was typically around 2.5%. For each patient the value for MAC was adjusted for the age of the patient (Gregory, Eger and Munson, 1969). The trachea was intubated with a gas-monitoring tracheal tube (Portex) 2–3 min after induction.

The lungs were ventilated via a non-rebreathing circuit at a flow of 100 ml kg^{-1} min^{-1} at a rate of 10 b.p.m. Such ventilation usually produces hypocarbia which would have reduced cardiac output and cerebral perfusion. In order to maintain this level of pulmonary ventilation, so enhancing the uptake of halothane, without producing hypocarbia, carbon dioxide was added to the inspired gas to maintain an end-expired concentration of 5% (Datex Normocap).

Ten minutes after the induction of anaesthesia the inspired concentration of halothane was adjusted to obtain a measured end-expired concentration of 1.5 MAC. This was maintained for 15 min and then reduced to 1.0 MAC for another 15 min. A third reduction to 0.5 MAC for 15 min was made before the sequence was repeated in reverse order (fig. 2). Surgery usually started between 10 and 15 min after the induction of anaesthesia.

The end-expired halothane concentration was measured with an Engstrom EMMA gas analyser placed at the origin of the expired limb of the circuit; a correction for the effect of expired water vapour was applied (Palayiwa and Evans, 1984).

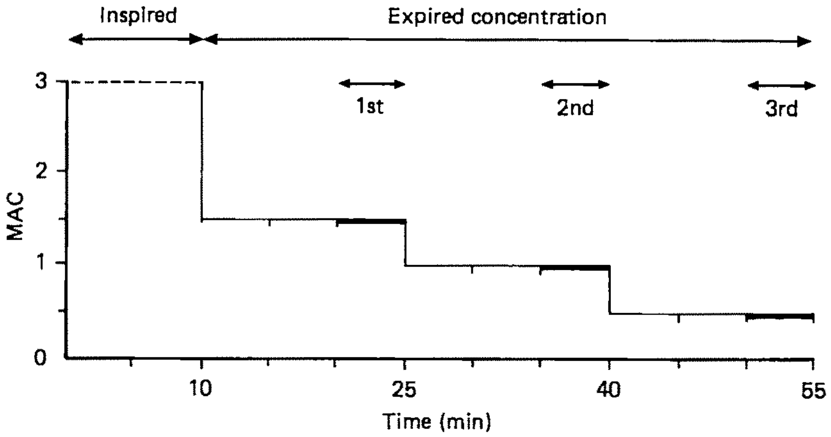

FIG. 2. A schematic illustration of the control of halothane concentration during the study. Initially inspired concentration was controlled, but end-expired concentration was measured after 10 min. Each step in the sequence consists of a 10-min equilibration and a 5-min measurement period, the first three of which are indicated.

Additional increments of pancuronium 0.1 mg kg^{-1} were given at intervals of 40 min. A crystalloid solution was infused i.v. at a rate of 1.0 litre h^{-1}.

Clinical monitoring

The adequacy of anaesthesia was constantly monitored by reference to clinical signs. A scoring system (based on systolic arterial pressure, heart rate, sweating and tears, the PRST score (see Appendix)) was used to assess and record the overall clinical condition of the patient (Evans and Davies, 1984). At 5-min intervals systolic arterial pressure, heart rate, amount of sweating and tears were noted. Each of these four indices was assigned a score value of 0, 1 or 2, producing a summed score having a range of 0–8. A sum PRST score in excess of 3 was taken as an indication to increase the end-expired halothane concentration to 1.5 MAC or, if the patient was already receiving 1.5 MAC, to 2.0 MAC. Thus the anaesthetic was controlled to try to maintain score values within the range 0–3. The sequence of exposures was then repeated in reverse order if time permitted.

LOC monitoring

The oesophageal probe was positioned (with the pressure sensing balloon 35 cm from the lips) after tracheal intubation had been completed. The oesophageal probe was similar in size and construction to a standard oesophageal stethoscope, except that it was provided with two sleeve-like balloons (fig. 3). The smaller distal balloon was water-filled and coupled via a narrow lumen to an external pressure transducer. The longer (5 cm) proximal balloon was coupled to a pneumatic system which intermittently inflated the balloon. Recording of LOC started approximately 10 min after the induction of anaesthesia. A permanent recording was made on a chart recorder and remained unseen by the anaesthetist. The pressure recordings were made over the range 0–100 mm Hg and the provoking cycle was set to inflate the balloon of the oesophageal probe for a period of 5 s every 90 s; the inflated balloon diameter was 15 mm. An oesophageal contraction was assumed to result from provocation if it was recorded within 10 s of the beginning of balloon inflation. This 10-s period represented 6.7% of the provocation cycle and some of the contractions may have been coincidental spontaneous contractions. The oesophageal monitoring system and probe were prototype systems developed for research purposes.

Data analysis

The analysis of the oesophageal pressure recordings was confined to the results obtained in the last 5-min period of each 15-min exposure; thus the first 10 min of the exposure period acted as an equilibration phase (fig. 2). When an exposure was abandoned (because of a PRST score greater than 3) and did not last for 15 min,

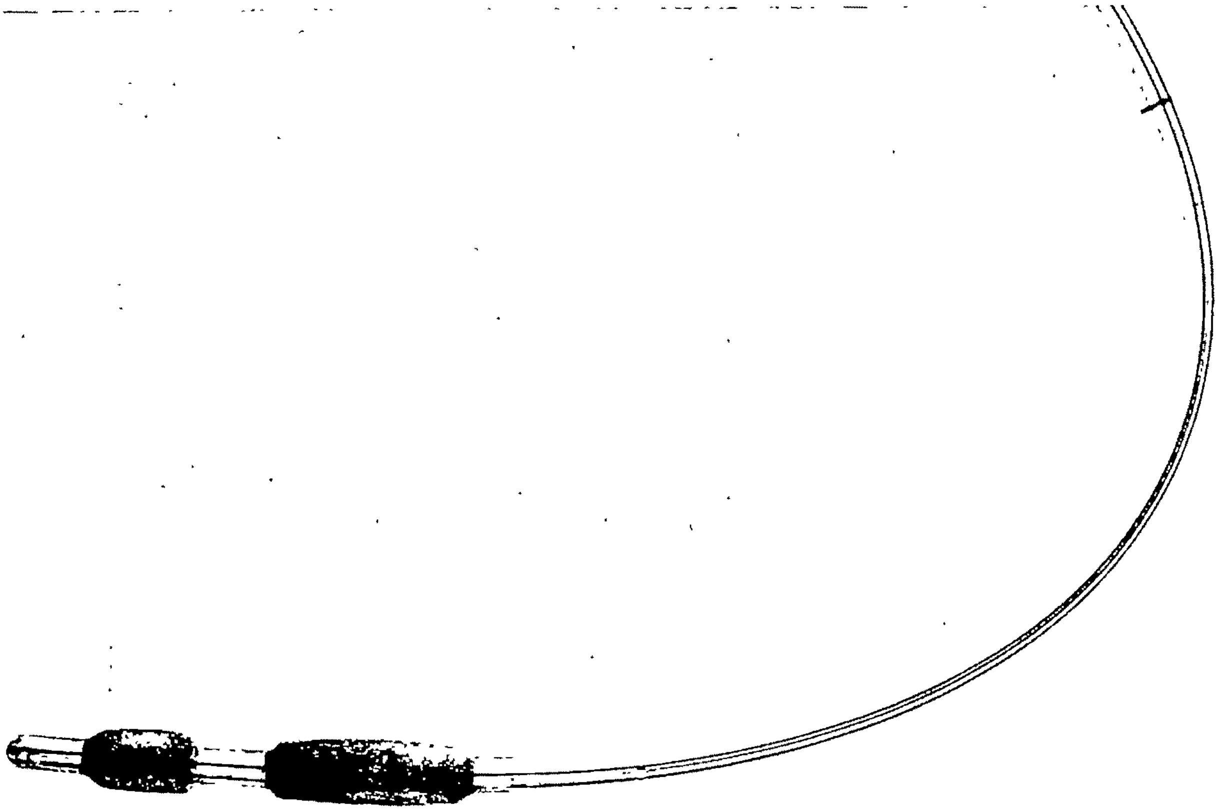

FIG. 3. The oesophageal probe. The marker is 35 cm from the distal pressure measuring balloon. The longer balloon is intermittently inflated to provoke a secondary peristaltic response.

the last 5-min period of that exposure was used for analysis; on some occasions this was the first 5 min of the exposure period. The results from such periods were assigned the MAC value with which the patient was being equilibrated. Such interruption of the sequence usually occurred during "step-down" in the end-expired halothane concentration. If the anaesthetic sequence had been allowed to continue it is probable that greater values for LOC indices and PRST score would have been recorded; additionally, the possibility of awareness would have been increased.

The 5-min section of the chart recording was examined to provide measures of the number of SLOC, the mean amplitude of SLOC and the magnitude of each PLOC. Only contractions exceeding 10 mm Hg above baseline were counted as SLOC. These results were recorded on analysis sheets, together with the PRST scores obtained at the beginning and end of the 5-min period and the relevant value of MAC. The results were examined to identify Pearson correlations between variables using SPSS software: R values are quoted as Pearson correlation coefficients. Student's t test was also used as appropriate.

Follow-up of patients

Patients were interviewed twice: first, in the recovery room and then on either the 2nd or 3rd postoperative day. Evidence of any postoperative discomfort arising from the use of the oesophageal probe was sought, as was any evidence of awareness during anaesthesia.

Design weaknesses

The investigation has several weaknesses in its design. These weaknesses tend to degrade the quality of the correlations being examined, but their elimination from the investigation was considered impracticable in this preliminary study.

The PRST scoring system was utilized so that a clinical index of the adequacy of anaesthesia could be incorporated to the study. The PRST scoring system is recognized to be far from perfect, but it represented a practical solution.

The exposure of patients to standardized concentrations of halothane, using MAC as a dose-setting index, has the disadvantage that an individual patient's sensitivity to the agent cannot be allowed for. Thus those patients who were particularly sensitive to the anaesthetic effect of halothane could be expected to be relatively deeply anaesthetized for any given dose as compared with those who were more resistant to the effect of halothane. The effect of age on MAC was allowed for.

Complete equilibration of the patient with the inspired gas mixture would take many hours and a compromise had to be accepted. The rate of equilibration was enhanced to a small extent by generous mechanical ventilation with added carbon dioxide, so ensuring that hypocarbia did not occur. An equilibration phase of 10 min for step changes of 0.5 MAC is relatively short, but was selected so that a sufficient number of samples could be obtained from each patient. In practice, the duration of surgery only allowed an average of four samples per patient.

The study would have been improved by the use of a less soluble volatile agent, such as isoflurane, and by the use of longer equilibration and sampling periods. The latter would have necessitated longer surgical procedures or perhaps slower surgeons! A means for assessing the MAC values of the individual patients would have been ideal.

RESULTS

Forty-six patients were studied (table I). The numbers and types of surgical operations are shown in table II. Correlations of patient characteristics (age, weight, height, tobacco consumption, alcohol consumption, premedication) and the magnitude of the maximum recorded values of SLOC rate and PLOC amplitude did not indicate any significant relationships between these patient characteristics and these indices of oesophageal activity.

TABLE I. *Details of patients studied* (n = 46)

Age (yr)	46.9 (SD 14.6)
Sex (M/F)	9/37
Weight (kg)	67.6 (SD 10.8)
Height (cm)	163.5 (SD 8.7)
Premedicated	12

TABLE II. *Surgical operations*

Procedure	*n*
Abdominal hysterectomy	10
Cholecystectomy	12
Abdominal hernia repair	11
Vaginal hysterectomy/repair	6
Varicose vein ligation/strip	3
Ovarian cystectomy	3
Prostatic resection	1

A total of 181 sets of results were analysed (a mean of almost four per patient, range 1–12). LOC was recorded in 43 of the 46 patients at some time during the recording period. In the three patients in whom no LOC was recorded, the maximum PRST scores were only 1, 1 and 2, despite exposure of two of those patients to 0.5 MAC for 15 min. Thus, despite exposure to a low concentration of anaesthetic agent, the clinical impression that the patients were well anaesthetized was associated with minimal oesophageal activity. A full 15-min exposure was not completed on 16 occasions because of an increase in the PRST score in excess of 3. Recalculation of the data with these patients excluded does not reveal a significantly different pattern of results.

Correlations of MAC and LOC derivatives with the two PRST scores (recorded at the beginning and end of the 5-min period) were strongest in the case of the second score. This, on reflection, is not surprising, since the changes in clinical signs would be expected to arise from preceding events that had recently occurred, for example changing surgical stimulus, during the preceding 5-min measurement period. Thus the second PRST is used as the preferred value in further correlations.

Clinical signs and MAC

The relationship between the PRST score and MAC is shown in figure 4. Between 2.0 MAC and 0.5 MAC there was an increase in mean PRST of 113%, although the difference between 1 MAC and 1.5 MAC was much smaller: the greatest

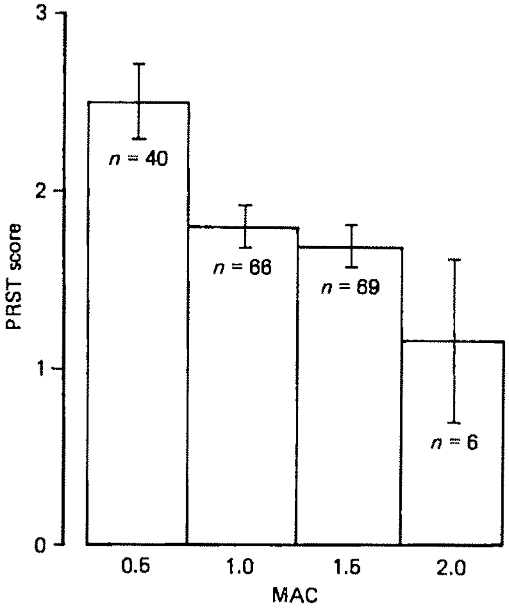

FIG. 4. PRST scores (mean, SEM) from recordings categorized according to MAC value. $P < 0.001$; $R = -0.27$.

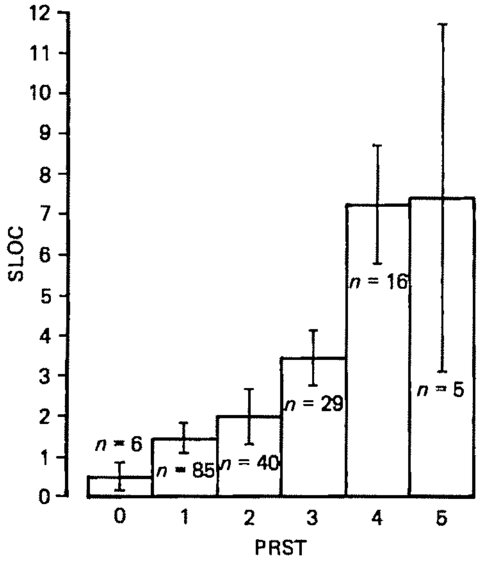

FIG. 5. SLOC rate (contraction min^{-5}) correlated with PRST scores (mean, SEM). $P < 0.001$; $R = 0.39$.

changes in PRST occurred at the extremes of the dose range.

Clinical signs and LOC

The relationships between PRST score and SLOC rate and PLOC amplitude are shown in figures 5 and 6. The ratio of SLOC rate at the highest and lowest PRST scores (5 and 0) was 10:1. The ratio of PLOC amplitude at the two score extremes was 5:1. The maximum value of PLOC has been used but the mean value has a similar correlation.

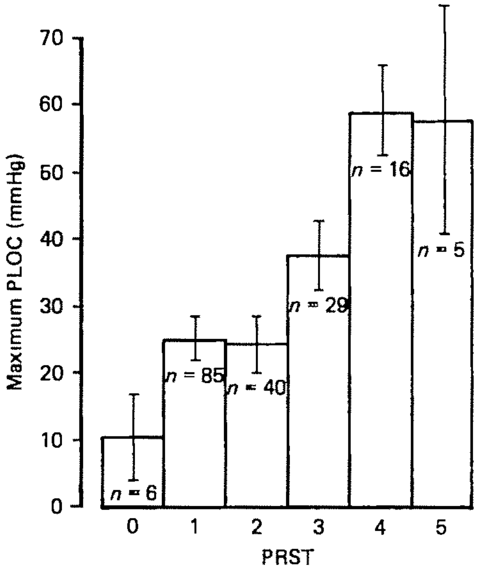

FIG. 6 Maximum PLOC response correlated with PRST score (mean, SEM). $P < 0.001$, $R = 0.35$.

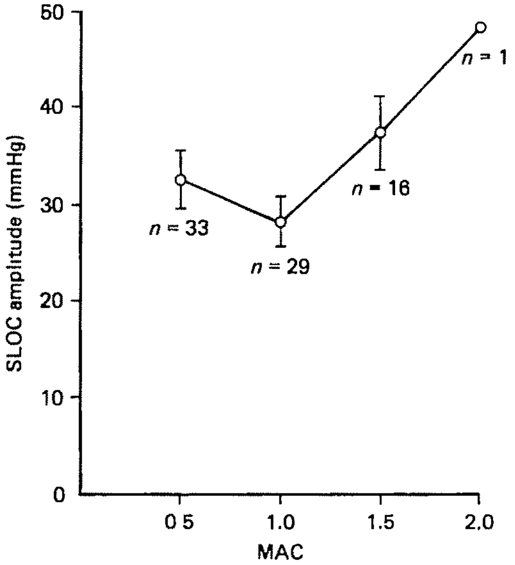

FIG. 7. Mean amplitude of SLOC correlated with halothane concentrations (mean, SEM). $P = 0.4$, $R = 0.09$.

LOC and MAC

There was no significant change in the mean

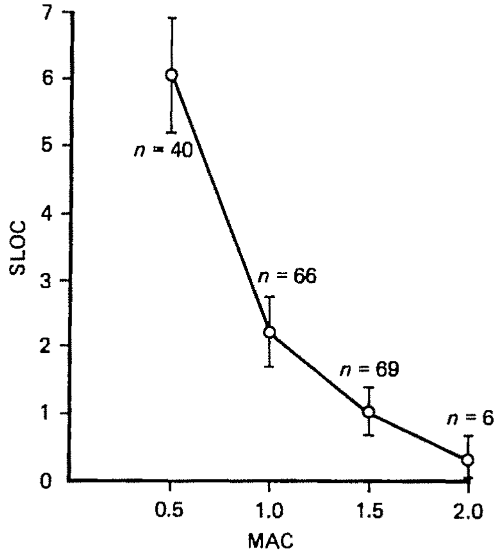

FIG. 8. SLOC rate (contractions min^{-5}) correlated with halothane concentration (mean, SEM). $P < 0.001$, $R = -0.40$.

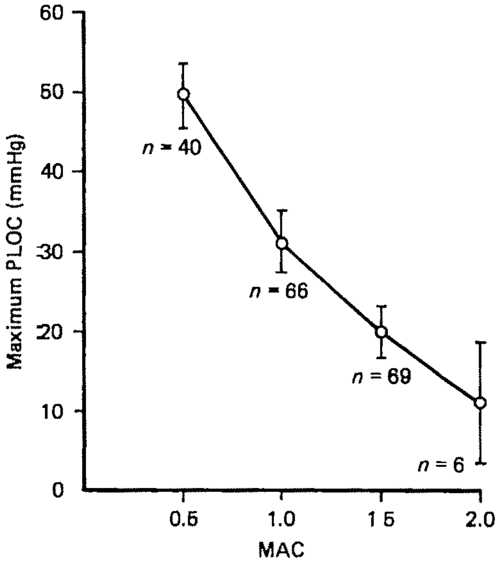

FIG. 9. Maximum PLOC response correlated with halothane concentration (mean, SEM). $P < 0.001$, $R = -0.37$.

amplitude of SLOC with changing dose of anaesthetic (fig. 7).

The correlations between MAC and SLOC rate and PLOC amplitude are shown in figures 8 and 9.

The ratio of SLOC rate between 0.5 MAC and 2.0 MAC was 15:1, while the ratio of PLOC amplitude over the same MAC range was 5:1.

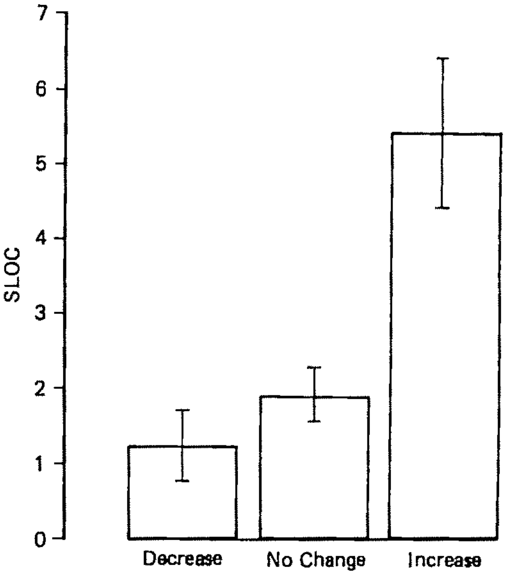

FIG. 10. Mean SLOC rate (contractions min^{-5}) in measurement periods when the PRST score either decreased ($n = 25$), remained unchanged ($n = 119$) or increased ($n = 37$). $P = 0.25$ decrease/unchanged; $P = 0.002$ no change/increase (Student's t test).

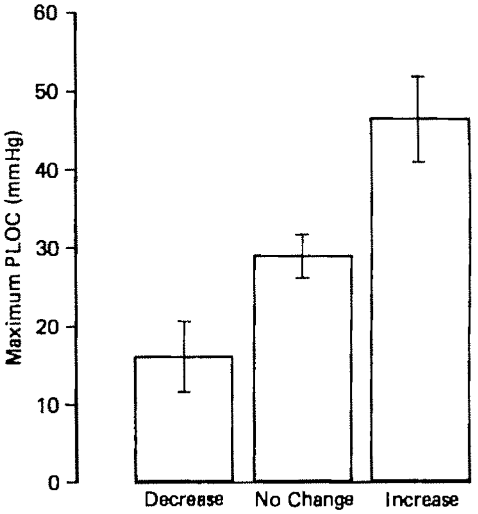

FIG. 11. Maximum PLOC in measurement periods when the PRST score decreased ($n = 25$), remained unchanged ($n = 119$) or increased ($n = 37$). $P = 0.018$ decrease/unchanged; $P = 0.007$ no change/increase (Student's t test).

LOC and surgical stimulus

During the investigation it was noted that the PRST scores recorded at the beginning and end of the recording period did not always remain constant, despite a relatively constant end-expired halothane concentration. The PRST score decreased on 25 occasions, increased on 37 occasions and remained unchanged on the remaining 119. It was assumed that the changes in the PRST score reflected a change in the level of surgical stimulus during the recording period. Figure 10 shows SLOC rate during the recording periods, categorized according to the change in PRST; similarly, figure 11 shows the changes in PLOC amplitude. It is clear that an increase in PRST score during the study period was associated with increases in SLOC rate and PLOC amplitude, and that a decrease in PRST score was associated with a decrease in these LOC indices.

On no occasion was any direct mechanical effect of surgical manipulations identified in the LOC recordings; even manual palpation of the lower oesophageal sphincter during exploration of the upper abdomen was without effect.

Patient follow-up

All patients were interviewed in the recovery room; 41 of the 43 patients were interviewed at the second postoperative follow-up. Two patients were lost as a result of early discharge. The incidence of postoperative sore throat was 37% and no patient complained of any postoperative symptoms that could be specifically ascribed to the use of the oesophageal probe. No patient had any recall of events during anaesthesia.

DISCUSSION

The investigation was designed to examine the relationships between LOC, clinical signs of anaesthesia and dose of anaesthetic. The investigation shows a clear relationship between these three variables.

An increasing alveolar halothane concentration was associated with a decrease in the PRST score. The control of anaesthesia was such that score values in excess of three would occur only occasionally. Thus the results relate to score values obtained in the lower half of the score range. Although significant, the correlations are not very strong. This is not surprising, given the weaknesses in the experimental design already referred to, and the fact that the PRST score is partly subjective and partly objective. Furthermore, for practical purposes the score values obtained were of a very limited range and subject to variation from observer error, and sources of interference. Pancuronium frequently gave rise to a tachycardia which was often reflected in the score. In addition, the PRST score was manifestly changed by changing levels of surgical stimulation. Although it would have been possible to use arterial pressure and heart rate alone as the parametric clinical variables in this investigation, they would have been subject to much variation from surgical stimulation. By assigning score values to them, this variation was to an extent reduced, but at the expense of a reduced fidelity of information. Since it was important to ensure that the patients could not become exposed to dangerously low concentrations of halothane, the control of the anaesthetic supply had to take into account other conventional clinical signs, notably sweating and lachrymation.

Both indices of LOC increased substantially as the PRST score increased. The increase in LOC activity was progressive over the range of PRST scores recorded. In the 62 measurement periods when the PRST score changed during relatively steady state anaesthesia, the changes in LOC and PRST again paralleled one another. This suggests that LOC is sensitive, not only to vapour concentration, but also to changing levels of surgical stimulation. During the investigation of LOC during anaesthesia outside of this study, it was apparent that changing levels of surgical stimulation will also produce changes in LOC. For the purposes of this study, the patients can be represented as a "black box" in which surgical stimulus, anaesthesia and the measured variables interact (fig. 12). Non-propulsive oesophageal activity is certainly stress-related (Faulkner, 1940; Nagler and Spiro, 1961; Rubin et al., 1962; Stacher, Schmierer and Landgraf, 1979), and the exposure of patients to low concentrations of vapour during surgery must provide a significant physiological stress. When the anaesthetic concentration is insufficient to maintain unconscious-

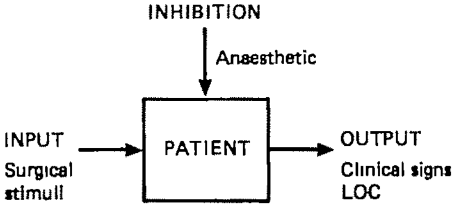

FIG. 12. The patient considered as a "black-box". The outputs (clinical signs and oesophageal activity) are a function of the inputs (surgical stimuli); the response of the patient is variably attentuated by anaesthesia.

ness, patients' recall of events frequently includes manifest evidence of great physiological and psychological stress (Bogetz and Katz, 1984).

This investigation confirms an earlier observation that, during anaesthesia produced by Althesin, anaesthetic dose affected SLOC rate, but did not affect SLOC amplitude (Evans, Davies and Wise, 1985). It might have been expected that increasing doses of halothane would have had a direct effect on smooth muscle and reduced the amplitude of the SLOC response. This did not occur over the dose range used which, together with the previous observation concerning Althesin, suggests that the direct effect of agents on the oesophageal musculature is minimal. The effect of nitrous oxide, halothane and enflurane upon lower oesophageal muscle tone has been studied (Sehhati, Frey and Star, 1980): it was found that these agents caused a small *increase* in tone of the lower oesophageal muscles. This contrasts with their effects upon the lower oesophageal sphincter, which became hypotonic. The SLOC response appears to be triggered as an "all or none" response (Evans, Davies and Wise, 1985). The fact that non-propulsive SLOC can be induced by psychological stress or acoustic stimulation (Stacher, Schmieter and Landgraf, 1979), considered with the fact that the oesophageal motility centre (dorsal vagal motor nuclei and adjacent reticular activating centre) lies in the brain stem, suggests that the likely site of action of the anaesthetic agent is in the brain stem (Inglefinger, 1958). In animals, vagotomy produces an initial suppression of all oesophageal motility; subsequently, local oesophageal reflexes progressively mature over days and some local peristaltic responses return (Cannon, 1907; Higgs and Ellis, 1965; Burgess, Schlegel and Ellis, 1972).

In contrast to SLOC, it is the amplitude of the PLOC response that correlates with the dose of anaesthetic. The isolated animal oesophagus is capable of generating a secondary peristaltic response and it can also be obtained in the denervated oesophagus *in vivo*. However, the evidence suggests that the secondary peristaltic response is not normally a local reflex, but is mediated via the oesophageal motility centre (Fleshler et al., 1959; Siegel and Hendrix, 1961; Janssens et al., 1974; Enzmann, Havell and Zboralske, 1977; Reynolds, El-Sharkawy and Diamant, 1985). Thus it is likely that the site of action of the anaesthetic agent upon the PLOC response is again in the brain stem. The similarity of the relationship between MAC value and the two LOC indices suggests a common control mechanism. Nishino and co-workers (1985) have demonstrated a comparable depression of the swallowing reflex during deepening nitrous oxide anaesthesia; the central control mechanism for swallowing lies in the motor nuclei of the hypoglossal nerve.

This preliminary study of the relationship between dose of anaesthetic, clinical signs and LOC has revealed many difficulties inherent in such a clinical investigation. There is no existing "gold standard" to refer to, and there is great diversity of opinion about the definitions of and means for estimating anaesthetic depth or adequacy. The relationships revealed in the present investigation suggest that LOC monitoring may have some potential value as a means of supplementing existing clinical signs as a means of controlling anaesthesia. The anaesthetic technique used in this investigation was far from conventional and, clearly, further investigation of more typical regimens should be undertaken, as must the effects of other non-anaesthetic drugs used during anaesthesia.

APPENDIX

Although no single clinical sign can be relied upon to behave consistently with anaesthetic requirements, the aggregate of clinical signs is used daily by anaesthetists to monitor and control anaesthesia. Clinical indices routinely used during anaesthesia include arterial pressure, heart rate, sweating, tears, pupil size and movement. Miosis is associated with both deep and very light anaesthesia and pupil size is markedly affected by the use of narcotic analgesics. Movement cannot be relied upon as an indicator in patients who are substantially paralysed by the use of neuromuscular blocking drugs. We have, therefore, used the first four clinical indices only upon which to base a simple scoring system (table III).

Such scoring systems have quite significant limitation and these are fully appreciated. However, the system represents a simple means of summating the significance of these widely recognized clinical signs. Each index is assigned a score of 0, 1 or 2 according to the conditions described in table III. Control values of arterial pressure and heart rate were obtained in the preoperative period.

The scoring system has nine levels of score, ranging from 0 to 8 and has substantial redundancy, in that summed scores above the midpoint are obtained infrequently. Thus for most applications a patient will be allocated to one of four score categories in the lower half of the score range.

The conditional limits upon pressure and rate shown in table III have been used, but these can be easily changed for other preferred values.

TABLE III. *Scoring system*

Index	Condition	Score
Systolic arterial pressure (mm Hg)	< Control + 15	0
	< Control + 30	1
	> Control + 30	2
Heart rate (beat min^{-1})	< Control + 15	0
	< Control + 30	1
	> Control + 30	2
Sweating	Nil	0
	Skin moist to touch	1
	Visible beads of sweat	2
Tears	No excess of tears in open eye	0
	Excess of tears in open eye	1
	Tear overflow from closed eyes	2

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A DOSE–RESPONSE STUDY WITH NALBUPHINE HYDROCHLORIDE FOR PAIN IN PATIENTS AFTER UPPER ABDOMINAL SURGERY

G. C. PUGH AND G. B. DRUMMOND

SUMMARY

Six male patients were studied on the morning following upper abdominal surgery for highly selective vagotomy. Nalbuphine hydrochloride was infused i.v. at different rates that increased progressively in each hour over a 4-h period. In the last 15 min of each hour, the plasma nalbuphine concentrations were almost steady (73–68, 71–82, 116–113 and 201–208 ng ml^{-1}). Patients and an observer made hourly assessments of pain and sedation. Although the changes in the pain and sedation scores were not significant, the patients' mean pain scores increased when the mean plasma nalbuphine concentrations were greater (> 82 ng ml^{-1}), which suggested that nalbuphine analgesia had been reversed. Nalbuphine caused sedation and possibly induced amnesia which could invalidate retrospective assessment, since the patients' assessment of analgesic efficacy at the end of the study was good. No cardiovascular depression or significant decrease in the ventilatory rate was recorded.

In the treatment of pain after surgery, a balance has to exist between the efficacy of an analgesic and its adverse effects. If the partial agonist–antagonist, nalbuphine hydrochloride, is effective in the treatment of severe pain, it may offer advantages over full agonists, since it causes less respiratory depression at higher doses (Romagnoli and Keats, 1980; Gal, DiFazio and Moscicki, 1982). However, partial agonists such as nalbuphine may reach a maximum analgesic effect (Gal, DiFazio and Moscicki, 1982; Eisele and Steffey 1984; Kay and Krishnan, 1986). Indeed, it has been suggested that nalbuphine-induced analgesia may be reversed at higher doses (Welch et al., 1980; Welch and Feldman, 1981). Infusion studies, in which stable plasma concentrations can be used to predict the concentration associated with pharmacodynamic action, have been advocated to test whether the high doses of agonist–antagonist opioids do provide improved analgesia (Eisele and Steffey, 1984).

This study aimed to assess the relationship between incremental increases in steady-state plasma nalbuphine concentrations and pain relief, sedation and the safety of nalbuphine—in patients after upper abdominal surgery.

PATIENTS AND METHODS

Six male patients (ASA grade I or II) were studied. They were aged between 19 and 60 yr and about to undergo highly selective vagotomy for peptic ulceration. Patients gave consent to the study, which included the reassurance that they could withdraw from the study or request alternative analgesia at any time without prejudice. The study was approved by the local ethics advisory committee.

The day before surgery patients answered questions about symptoms that could result from the administration of an analgesic. The same questions were repeated at the end of the study for comparison. The linear analogue method for measuring pain and sedation was explained.

Anaesthesia and the period before the dose–response study

Patients received temazepam 20 mg orally 1–2 h before surgery. Anaesthesia was induced with

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G. C. PUGH, B.SC., M.B. CH.B., D.R.C.O.G., M.R.C.G.P., D.A., F.F.A.R.C.S.; G. B. DRUMMOND, M.A., M.B. CH.B., F.F.A.R.C.S.; Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW.

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thiopentone 5–7 mg kg^{-1} i.v. and tracheal intubation was facilitated with suxamethonium 1.5 mg kg^{-1}. Anaesthesia was maintained with 66% nitrous oxide and enflurane in oxygen. Nalbuphine 20 mg i.v. was given during surgery. Neuromuscular blockade was achieved with alcuronium and antagonized, on completion of surgery, with neostigmine 2.5 mg (plus atropine 1.2 mg). About 15 min after the induction of anaesthesia, an i.v. infusion of nalbuphine 2 mg kg^{-1}/24 h in 5% dextrose was started, from a clockwork infusion pump (Handley), modified for 24-h delivery.

In the recovery room, patients received nalbuphine 10 mg i.v. at 5-min intervals until analgesia was achieved. In the ward, the ventilatory rate was counted over 1 min and recorded hourly. Each patient could be given nalbuphine 10 mg i.m. every 2 h, if required for pain, in addition to the infusion.

Nalbuphine dose–response infusion

At 06.00 h (−60 min) on the morning following the day of the operation, the overnight nalbuphine infusion (2 mg kg^{-1}/24 h) was discontinued. A second nalbuphine infusion (dose–response infusion) was commenced 1 h later (time zero) using an electronic digital syringe pump (Vickers, Treonic IP4, model No. 118). Patients were unaware of the change in nalbuphine infusion or of the subsequent changes in dose.

The initial dose of nalbuphine during the first 1 h was 1 mg kg^{-1}/24 h (fig. 3A). For the first 6 min of the second hour, the infusion rate was increased to 10 mg kg^{-1}/24 h (loading dose) and then reduced to 2 mg kg^{-1}/24 h for the remaining 54 min. In the third hour, the infusion rates for the 6- and 54-min periods of the previous hour were doubled, and then doubled again in the fourth hour. The intention of this procedure was to reach a stable nalbuphine plasma concentration at the end of each hour of infusion (times 60, 120, 180 and 240 min) which was related in a logarithmic manner to the preceding values. The mean total dose of nalbuphine administered during the 4-h dose–response infusion was 61.8 mg (range 48.0–72.2 mg).

Nalbuphine assay

Venous blood samples (10 ml) were taken at the following times: zero, 45, 60, 105, 120, 165, 180, 225, 240 and 300 min. The samples were taken 15 min apart to indicate how well plasma steady-state concentrations had been achieved during that 1 h of the infusion. Nalbuphine serum concentrations (ng ml^{-1}) were estimated by high pressure liquid chromatography. The assay was sensitive to 1 ng ml^{-1} and specific for nalbuphine with no cross reaction with metabolites. The coefficient of variation was < 2% for nalbuphine concentrations > 6 ng ml^{-1}. Nalbuphine concentrations in serum and plasma are identical (Aitkenhead A. R. and Achola K. J., personal communication) and in this paper the term "plasma" has been used to describe the measured "serum" concentrations.

Patient and observer assessments of pain and sedation

Patients were confined to bed for the period of the dose–response infusion. Routine nursing care was given, but conversation and reassurance were kept to a minimum so as not to influence the assessments. The assessments were performed by one observer (G.C.P.) who remained with each patient throughout the study.

Patients marked a horizontal (100-mm) linear analogue scale (LAS) to asssess the degree of pain (between "no pain" and "worst pain") and sedation (between "alert" and "drowsy") at −60 min, zero and at the end of each hour at 60, 120, 180, 240, 300 and 360 min. At the same times, the observer assessed patients' pain with a scale related to movement (Prince Henry Pain Scale, PHPS: 0 = no pain on coughing; 1 = pain on coughing, but not on deep breathing; 2 = pain on deep breathing, but not at rest; 3 = some pain at rest, slight; 4 = pain at rest, severe (Torda and Pybus, 1984)) and sedation with a 4-point scale (1 = awake and normal; 2 = drowsy; 3 = sleepy, needs to be spoken to; 4 = sound asleep). The effect of decreasing nalbuphine plasma concentrations was determined by assessing pain and sedation for 2 h after the end of the dose–response infusion.

Patients gave an assessment of the effectiveness and tolerance of their analgesic treatment (4 = excellent, 3 = good, 2 = fair, 1 = poor) following surgery at 360 min.

Cardiovascular and ventilatory assessments

Arterial pressure was measured by the Riva-Rocci method and recorded every 0.5 h along with heart rate until 2 h after the infusion (360 min). Ventilatory rate was counted over 1 min and recorded every 0.5 h.

Chest physiotherapy was performed on those patients who had evidence of sputum retention. Patients were examined for signs of chest infection at 360 min. The criteria for chest infection were: pyrexia (temperature > 37 °C), spontaneous coughing, expectoration of purulent sputum and any abnormality detected on auscultation of the lungs. Chest infection was diagnosed if three or all of these features were present.

Statistics

The results were expressed as mean (SD). Statistical analysis was by the Wilcoxon rank sum test.

RESULTS

Each operation was performed by the same surgeon, through a midline upper abdominal incision. The physical characteristics of patients are summarized in table I. Five patients were taking either regular cimetidine (Nos 2 and 3) or ranitidine (Nos 4, 5 and 6).

Period before the dose–response study

The mean total dose of nalbuphine administered from operation to 06.00 h (mean 18.8 h) was 183.6 (55.5) mg (range 113.3–245.0 mg). The cumulative doses of nalbuphine, administered to each patient, are illustrated in figure 1. Three patients (Nos 4, 5 and 6) required frequent administration of nalbuphine for severe pain on recovery from anaesthesia. One (No. 6) required nalbuphine 60 mg i.v. over a period of 30 min. On the ward, another patient (No. 3) continued to have pain after nalbuphine i.m. (total 20 mg) within 2 h of surgery and required i.v. injections of nalbuphine (total 80 mg) over a period of 45 min. These doses of nalbuphine caused profound sedation. No cardiovascular depression or significant change in the ventilatory rate was recorded during this period. No patient requested alternative analgesia or withdrawal from the study.

TABLE I. *Physical characteristics of patients studied. Ideal weights from* Statist. Bull Metro. Life Insur. Co., 40, *Nov–Dec 1959*

Subject	Age (yr)	Wt (kg)	Ht (cm)	Wt/Ideal wt
1	51	83	175	1.07
2	23	67	185	0.93
3	34	82	183	0.97
4	48	56	173	0.89
5	60	76	163	1.13
6	19	67	178	1.01

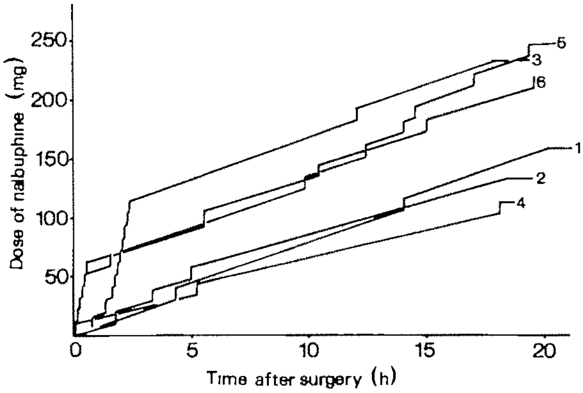

FIG. 1. Individual cumulative nalbuphine dose curves for the interval between the end of surgery and the start of the dose–response study.

Nalbuphine dose–response study: plasma concentrations

The nalbuphine plasma concentration profiles for each patient were similar (fig. 2). Three patients (Nos 4, 5 and 6) required nalbuphine 10 mg i.m. for pain, within 10 min of stopping the first infusion at −60 min, but plasma concentrations in these patients at the start of the dose–response infusion were not greater than in the other patients. The initial plasma concentrations (time zero) showed a wide variation (range 37–145 ng ml^{-1}). The mean nalbuphine plasma concentration decreased over the first 60 min, but increased again at 120 min with values similar to the initial mean plasma concentration (table II, fig. 3B). This was consistent with stopping the overnight infusion (2 mg kg^{-1}/24 h) for 60 min and starting the dose–response infusion at a slower rate (1 mg kg^{-1}/24 h). The mean plasma concentration then increased from 120 min to the end of the infusion in a log linear manner (r = 0.86) (fig. 3B). In the last 15 min of each hour, the mean plasma concentrations were 73–68, 71–82, 116–113 and 201–208 ng ml^{-1} which, as a percentage of the concentration at the end of each hour, represented a change of only 7.3, 13.4, 2.7 and 3.3% within the last 15 min.

The plasma nalbuphine concentration from one patient (No. 4) at 240 min was unexpectedly low (58 ng ml^{-1}) (fig. 2). The reason for this is not clear, but the infusion tubing may have become disconnected in the final hour of the infusion. As

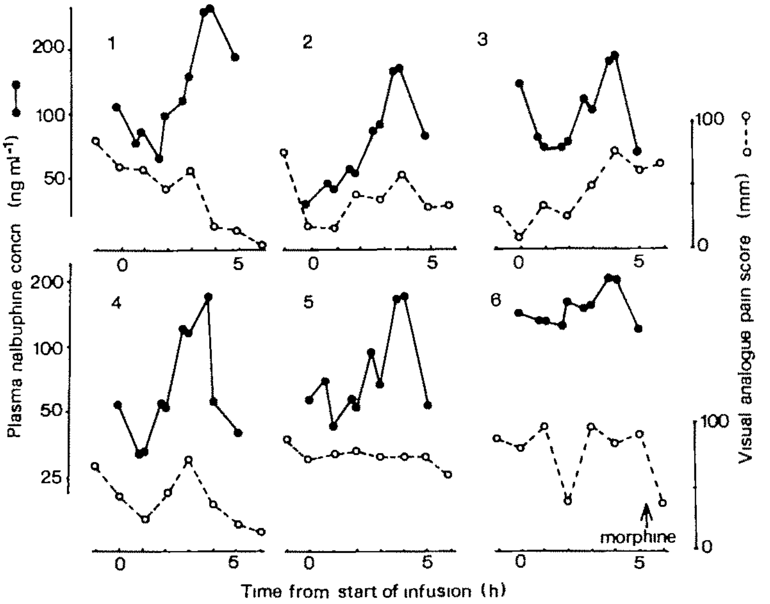

FIG. 2. Individual plasma nalbuphine concentration profiles (closed symbols and continuous lines) related to the subjective pain scores (open symbols, interrupted lines). The patient numbers 1 to 6 correspond to the text.

TABLE II. *Mean (SD) values for plasma nalbuphine concentration (ng ml^{-1}), patient pain and sedation (LAS), and observer pain (PHPS) and sedation scores during the dose-response study.*
**Patient No. 4 omitted from 240 min; **patient No. 6 omitted from 360 min*

	Time (min)							
	−60	zero	60	120	180	240*	300	360**
Nalbuphine concn (ng ml^{-1})		90(46)	68(36)	82(45)	113(33)	208(59)	93(52)	
Pain LAS	72(22)	49(33)	54(31)	47(18)	66(21)	63(27)	49(32)	36(28)
Sedation LAS	48(31)	67(22)	70(20)	55(21)	59(24)	70(23)	42(27)	63(32)
PHPS	3.5(0.6)	3.3(0.5)	3.3(0.8)	2.8(0.8)	3.0(0.9)	2.6(1.1)	2.2(1.5)	1.8(1.1)
Sedation score	1.8(0.4)	2.3(0.8)	2.5(0.8)	2.2(0.8)	2.5(0.8)	3.0(0)	2.2(0.8)	2.0(0)

a steady state concentration had not been achieved in the final hour, the plasma nalbuphine concentrations from this patient were not included in the mean plasma concentrations at 225 and 240 min. The response of this patient to the decrease in the plasma nalbuphine concentration is discussed.

Patient pain scores (LAS)

No significant change in pain scores was demonstrated. However, some of the trends observed were of interest. At the start of the study (−60 min), patients recorded high pain scores (mean 72) (table II, fig. 3C). In the subsequent hour, when no drug was being infused, each patient recorded a decrease in pain score (fig. 2). The mean pain scores showed a tendency to increase at the greater plasma nalbuphine concentrations.

Patient No. 4 was not included in the mean pain score at 240 min as a steady plasma nalbuphine concentration had not been reached in the final 1 h of the infusion. In this patient the decrease in the plasma concentration (from 123 to 58 ng ml^{-1}) at 180 min and 240 min coincided with a marked decrease in the pain score (73 to 37) (fig. 2) and PHPS (4 to 1). This fortuitous event supports the conclusion that pain relief may be greater at

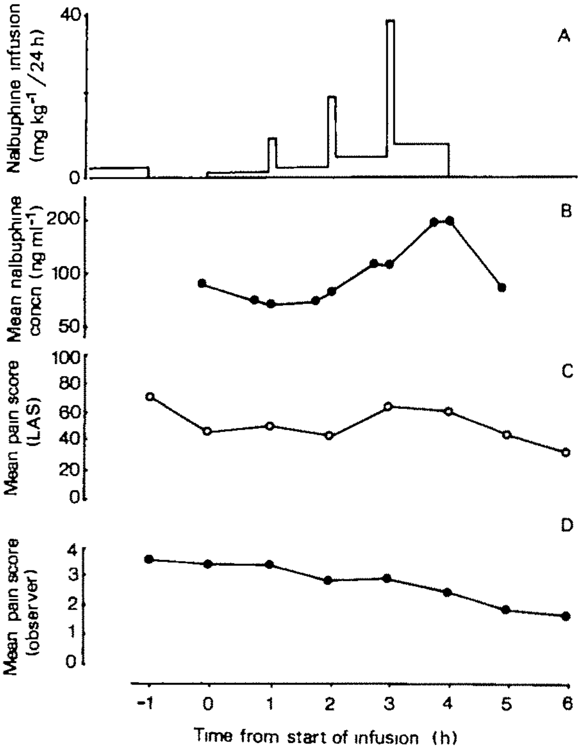

FIG. 3. A: Dose–response infusion regimen. B: Mean plasma nalbuphine concentration (logarithmic scale). C: Mean pain score (linear analogue (LAS), open symbols). D: Mean observer pain score (PHPS, closed symbols).

lower nalbuphine plasma concentrations (< 100 ng ml^{-1}).

Observer pain scores (PHPS)

There were no significant changes in the observer pain scores. The mean score was greatest (3.5) at -60 min (table II, fig. 3D), in accordance with the high patient mean pain LAS at the same time. At the start of the dose–response infusion, the mean pain score decreased (3.3) and remained constant over the next 3 h of the infusion (3.3, 2.8 and 3.0). The mean score decreased (2.6) at 240 min (fig. 3D).

Sedation scores

No significant change in the sedation scores was demonstrable (table II). Marked sedation was present throughout the study. The patients' mean sedation score was greatest at 60 and 240 min (fig. 4).

The observer recorded high sedation scores at the start of the study which increased during the dose–response infusion, reaching a maximum at 240 min (fig. 4). Each patient was able to be aroused, when spoken to, at the time of maximum sedation. The effect of sedation on the patients' ability to complete the pain and sedation LAS was difficult to assess. No patient failed or needed help to complete the LAS.

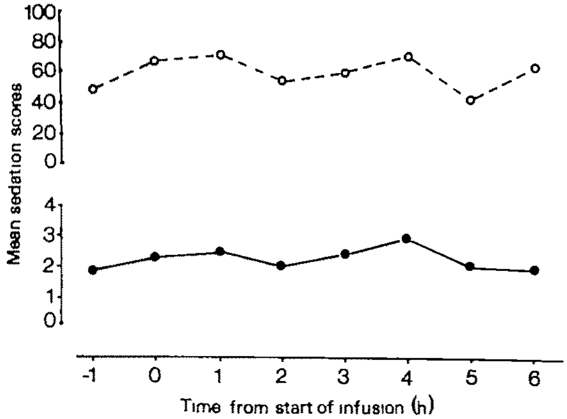

FIG. 4. Mean linear analogue (○) and observer (●) sedation scores.

Assessments after the dose–response infusion

As part of their routine mobilization regimen, patients were sat out of bed 30 min after the end of the dose–response infusion (except patient No. 6), and this change of posture may have influenced the assessments of pain and sedation. The mean patient and observer pain scores decreased 1 h after completion of the infusion (49 and 2.2, respectively) which coincided with a decrease in the mean plasma nalbuphine concentration (fig. 3). Patient No. 6 was excluded from the final assessments of pain and sedation, at 360 min, as alternative analgesia was given on request at 310 min. The remaining patient (36) and observer (1.8) mean pain scores showed a further decrease at 360 min.

The mean patient sedation score decreased (42) 1 h after the end of the dose–response infusion and increased (63) 1 h later at 360 min (fig. 4). The observer sedation scores continued to decrease in the 2 h after the end of the dose–response infusion (2.2 and 2.0).

Cardiovascular and ventilatory assessments

The systolic and diastolic arterial pressures and heart rate remained stable throughout the dose–response infusion study (mean range (SD): systolic 144–154 (14–20) mm Hg; diastolic 85–91 (4–19) mm Hg; heart rate 80–90 (8–15) beat min^{-1}).

Five patients (Nos 1–5) required physiotherapy, during the dose–response infusion; this was performed shortly after an assessment. Patients were more comfortable following physiotherapy as their need to cough was reduced. Patient No. 6 had no cough, so physiotherapy was delayed until alternative analgesia had been given at 310 min. Four patients (Nos 1, 2, 4 and 5) were cigarette smokers and were assessed as having a chest infection.

No depression of the ventilatory rate was observed with nalbuphine (mean range 17–20 b.p.m.).

Patient assessment of efficacy, tolerance and side effects

Five patients gave their assessment of the efficacy and tolerance of the treatment given for pain from operation to completion of the study at 360 min. One patient (No. 6) gave his assessment at 310 min before receiving alternative analgesia. In contrast to the pain scores, these retrospective assessments were equally divided between excellent (Nos 4 and 5), good (Nos 1 and 2) and fair (Nos 3 and 6).

The tolerance scores were: good (Nos 1, 5 and 6), fair (Nos 3 and 4) and poor (No. 2), which were related to the number of adverse effects reported: 1 (No. 1), 3 (No. 5), 4 (No. 6), 6 (Nos 3 and 4) and 10 (No. 2). The adverse effects were not limited to analgesic side effects (drowsiness, dry mouth, sweating, dizziness, difficulty in remembering, sore throat, nausea, feeling hot, blurred vision, hearing problems, excessive thirst, urinary problems, limb stiffness and depression).

DISCUSSION

The number of patients in this study was small. However, it was considered ethically unacceptable to continue the study as it became clear from other studies that nalbuphine provided inadequate analgesia in a high proportion of patients who had undergone abdominal surgery (Kay and Krishnan, 1986; Pugh et al., 1987).

Period before the dose–response study

Nalbuphine was the only analgesic administered to patients before the dose–response study. Half the patients required frequent administration of nalbuphine for severe pain on recovery from anaesthesia. No patient requested to be withdrawn from the trial or asked for alternative analgesia. The observer considered withdrawing three patients, but allowed them to continue in the study when additional nalbuphine caused increased sedation and the patients appeared to "settle". Although the larger doses of nalbuphine appeared to increase sedation without a commensurate increase in analgesia, no formal testing of pain and sedation was performed. The mean total dose of nalbuphine administered between surgery and the dose–response study represented more than three times the dose of nalbuphine given to patients, following cholecystectomy, by Bahar, Rosen and Vickers (1985). The difference may reflect the greater pain experienced after vertical upper abdominal incisions. Greater doses of nalbuphine have been administered to patients following abdominal surgery, in whom analgesia was unsatisfactory in a large proportion (Kay and Krishnan, 1986).

Dose–response study

The influence of anaesthesia on the assessment of the patients was decreased by performing the dose–response study the day after surgery. The accurate assessment of pain relief by patients after surgery is notoriously difficult, but changes in linear analogue scores remain one of the best subjective methods of pain measurement (Revill et al., 1976). Our patients were able to record pain scores at each assessment. However, the effect of sedation on the reliability of these scores is difficult to assess. It has been suggested that pain during movement may be a useful discriminator between analgesics (Bahar, Rosen and Vickers, 1985). A scale relating pain to movement (PHPS) was used. However, when patients complained of pain between "severe" and "slight" the scale was not sensitive enough; therefore, observer bias could not be excluded. The patient sedation scores could be considered less appropriate than the observer sedation scores as each patient had to be disturbed to allow an assessment to be made.

Few studies have attempted to relate plasma analgesic concentrations to the antinociceptive effects following surgery. This study achieved steady mean plasma nalbuphine concentrations at the end of each hour of the dose–response infusion. Therefore, pharmacodynamic effects were assumed to be constant at these times. Despite the significant increase in plasma nalbuphine concentration, pain scores did not change significantly. Although the pain LAS values were very variable, an unexpected finding was that pain increased at the higher nalbuphine plasma concentrations—a feature which supports the clinical impression gained by Welch and Feldman (1981). The mechanism of action of nalbuphine at the receptor is not understood clearly. An inverse response curve for analgesia has been discussed (Jasinski, 1983) and may explain the pharmacodynamic effects of nalbuphine in terms of either a two-receptor theory or a form of acute tolerance. The two-receptor theory attempts to explain the reduction of analgesia at higher doses, by suggesting that the drug acts at a second receptor, which produces physiological antagonism to the first. If there is a drug concentration–receptor occupancy relationship, as the plasma concentration decreases again, analgesia should return along the same path (Hull, 1983). Our results suggested that analgesia improved as the plasma nalbuphine concentration decreased.

Analgesic studies (Bullingham, 1983 from drug company data) have suggested that a plasma nalbuphine concentration of 20 ng ml^{-1} exerts a significant pharmacological effect. In the present study a mean plasma nalbuphine concentration greater than 82 ng ml^{-1} was associated with a greater patient pain score, and supports the findings of Welch and colleagues (1980). Kay and Krishnan (1986) have suggested that the efficacy of nalbuphine analgesia runs parallel to its respiratory effects, and that a maximum degree of analgesia is obtained, probably at a dose somewhere between 0.3 and 0.5 mg kg^{-1}. Gal, DiFazio and Moscicki (1982) administered nalbuphine i.v. to six healthy volunteers who were subjected to experimental pain. The mean pain tolerance reached a maximum at the lowest plasma concentration (24 ng ml^{-1}) and in two of the subjects pain increased at the greater plasma concentration (62 ng ml^{-1}).

Sedation is a recognized feature of treatment with nalbuphine (Forrest, 1971; Beaver and Feise, 1978) and was marked throughout this study. The observer rated pain as least at the highest plasma concentration, when the greatest degree of sedation was present. The patients, however, recorded increased pain associated with the greater plasma nalbuphine concentrations, at a time when they felt sleepy. The difference between the patient and observer pain scores, at the greatest plasma nalbuphine concentration, may possibly have been because the observer was unable to distinguish analgesia from sedation. Three patients would have been withdrawn from this study, if sedation had not given the impression that they were "settled". One patient recorded high pain scores throughout the study, but did not request additional or alternative analgesia until 1 h after the nalbuphine infusion had been discontinued, when his sedation had decreased.

Amnesia following the administration of nalbuphine has not been widely reported, but was noted by Kay and Krishnan (1986) in a study with large doses of nalbuphine in patients following abdominal surgery. Patients in our study complained of severe pain and recorded high pain scores on a number of occasions, yet at the end of the study, four of the six patients indicated that their analgesia since operation had been good or excellent. This apparent paradox may be explained if the patients had forgotten the severe pain earlier or had been influenced by the improved level of pain relief at the time of the assessment. One patient complained of nausea which required i.m. medication on two occasions, but failed to remember this when questioned at the end of the study. An amnesic effect is supported by our observations in a separate study with nalbuphine for pain after operation. Patients who had been withdrawn because of inadequate analgesia, despite large doses of nalbuphine, failed to remember the severe pain in the immediate postoperative period when questioned the following day (Pugh et al., 1987). Analgesics which cause amnesia may give misleading results if studies depend on retrospective assessments. This supports the criticism of single 24-h assessments of analgesia (Kay, 1985; Smith, 1985).

Cardiovascular stability was observed, as in earlier studies (Fahmy, 1980; Lake et al., 1982). The ventilatory rate did not alter as the nalbuphine plasma concentration increased, suggesting that respiratory depression was not a major feature of the use of nalbuphine (Romagnoli and Keats, 1980; Gal, DiFazio and Moscicki, 1982). Sedation and dry mouth were the most commonly reported side-effects; no serious side-effects were observed.

Nalbuphine may not posses a strong positive dose–response relationship. This study suggests that, if satisfactory analgesia is not obtained in some patients with low doses of nalbuphine, improvement may not necessarily occur with additional doses. Heavy sedation is a feature of high doses of nalbuphine and this hampers the assessment of analgesia.

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CONSTANT I.V. INFUSIONS OF NALBUPHINE OR BUPRENORPHINE FOR PAIN AFTER ABDOMINAL SURGERY

G. C. PUGH, G. B. DRUMMOND, R. A. ELTON
AND C. C. A. MACINTYRE

SUMMARY

A double-blind, sex-stratified, study compared the analgesic efficacy and side effects of nalbuphine 10 mg ml^{-1} (group N) and buprenorphine 0.15 mg ml^{-1} (group B) administered as a continuous infusion (0.2 ml kg^{-1}/24 h), after abdominal surgery. Patients could request additional i.m. analgesic for pain. The study groups were well matched. The trial was stopped after 55 patients had been studied (nalbuphine 29, buprenorphine 26), because nine patients in the nalbuphine group had inadequate pain relief ($P < 0.01$) shortly after surgery (mean 2.5 h). Analysis of the results on an "intention to treat" basis showed that the patients who received buprenorphine had significantly greater pain relief at 1, 3, 6 and 20 h after surgery. Patients who received buprenorphine were assessed by the physiotherapist to have less pain and better chest expansion. More additional analgesic was given to the patients receiving nalbuphine. In the patients receiving buprenorphine, the mean ventilatory rate was less (N = 19 b.p.m., B = 14 b.p.m.) ($P < 0.001$) and the increase in Pa_{CO_2} was greater (N = 0.5 kPa, B = 1.1 kPa) ($P < 0.001$), compared with the value before operation. Side effects were equal, and no serious adverse effects were observed in either group.

The agonist/antagonist, nalbuphine hydrochloride, is recommended for the relief of moderate to severe pain and has been reported to provide effective analgesia following a variety of surgical procedures (Tammisto and Tigerstedt, 1977; Beaver and Feise, 1978; Bahar, Rosen and Vickers, 1985). Other studies, however, have failed to show improved analgesia with nalbuphine when compared with other opioids (Wayne and Braunfield, 1982; Brady, Furness and Fee, 1986) and nalbuphine has insufficient activity to be adequate as a sole agent for surgical anaesthesia in patients having cardiac surgery (Lake et al., 1982). The usefulness of nalbuphine as an analgesic may be limited by either a small "Effect maximum for analgesic efficacy" (E'a max) (Kay and Krishnan, 1986) or the possible antagonism of analgesia at higher doses (Welch and Feldman, 1981; Gal, DiFazio and Moscicki, 1982; Eisele and Steffey, 1984).

The aim of this study was to assess the analgesic efficacy and side effects of nalbuphine (N) in a comparative study with buprenorphine (B), administered as a continuous infusion for 20 h, in patients following abdominal surgery.

PATIENTS AND METHODS

One hundred patients (ASA I or II) aged 18–75 yr and scheduled for elective abdominal surgery were assigned randomly to receive nalbuphine or buprenorphine, as a constant infusion i.v., during anaesthesia and for 20 h following surgery. The study was double-blind, stratified for sex and designed so that each patient had the opportunity of achieving a similar degree of analgesia. Patients gave informed consent for the study which was approved by the local ethics committee.

G. C. PUGH, B.SC., M.B., CH.B., D.R.C.O.G., M.R.C.G.P., D.A., F.F.A.R.C.S.; G. B. DRUMMOND, M.A., M.B., CH.B., F.F.A.R.C.S.; Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW. R. A. ELTON, PH.D.; C. C. A. MACINTYRE, M.SC.; Medical Statistics Unit, Medical School, Teviot Place, Edinburgh EH8 9AG. Accepted for Publication: May 26, 1987.

Correspondence to G.C.P.

Assessments before surgery

Patients were visited by one investigator (G.C.P.) the day before surgery. Patients' age, height, weight, the number of previous hospital admissions and general anaesthetics, smoking habits, alcohol consumption, and ASA physical status were noted. The systolic and diastolic arterial pressures, heart rate and any ECG abnormalities were recorded. Each patient completed an Eysenck Personality Questionnaire (Eysenck and Eysenck, 1984) and a State–Trait Anxiety Inventory (Spielberger, 1977). Patients answered questions about symptoms that could result from analgesic administration. The same questions were repeated 20 h after surgery for comparison. The linear analogue method (LAS) for measuring pain was explained to patients.

Physiotherapy assessment

Each patient was visited the day before surgery by the physiotherapist who assessed patients for: mobility (4 = good (normal), 3 = moderate, 2 = fair, 1 = poor); ability to cough (3 = effective, 2 = effective with help, 1 = ineffective); chest expansion (4 = good (normal), 3 = moderate, 2 = fair, 1 = poor); level of pain during physiotherapy (1 = severe, 2 = moderate, 3 = mild, 4 = none); and the physiotherapist's assessment of patient's performance (1 = excellent, 2 = good, 3 = moderate, 4 = fair, 5 = poor). The assessments were repeated about 20 h after surgery, by the same physiotherapist.

Preparation of trial analgesics

Nalbuphine 10 mg ml^{-1} was considered equipotent with buprenorphine 0.15 mg ml^{-1} (potency ratio 66:1). Syringes containing nalbuphine 200 mg in 20 ml and 10 mg in 1 ml, or buprenorphine, diluted with 5% dextrose, 3 mg in 20 ml and 0.15 mg in 1 ml, were prepared by the hospital pharmacy. The analgesics were stored at 4 °C for a maximum of 7 days.

Anaesthesia and analgesia

Premedication was with temazepam 20 mg by mouth 1–2 h before surgery. Anaesthesia was induced with thiopentone 5–7 mg kg^{-1} and intubation of the trachea facilitated with suxamethonium 1.5 mg kg^{-1}. Anaesthesia was maintained with a volatile agent (usually enflurane) in 66% nitrous oxide and oxygen. The appropriate trial analgesic (0.5–3.0 ml i.v.) was given as indicated for suppression of hypertension or tachycardia during surgery. An i.v. infusion of the trial analgesic (0.2 ml kg^{-1}/24 h) in 5% dextrose (total volume 20 ml) was started within 15 min of induction of anaesthesia and continued for 20 h after surgery, using a clockwork infusion pump (Handley), modified for 24 h delivery. Muscle paralysis was maintained with a non-depolarizing agent (usually alcuronium) and antagonized with neostigmine 2.5 mg (plus atropine 1.2 mg). The recovery time, from the end of anaesthesia to patient obeying commands, was recorded.

In the recovery area, patients were given i.v. injections of the trial analgesic (1 ml), every 5 min, until pain relief was achieved. Patients then returned to the ward where the trial analgesic could be given (1 ml i.m.) every 2 h, as required for relief of pain, in addition to the constant infusion. Patients who continued to complain of pain despite additional i.m. analgesia were given i.v. injections of the trial analgesic (1 ml) every 5 min until a maximum of 10 ml of additional analgesic had been given.

After the continuous infusion of the trial analgesic ended, further analgesia was provided with sublingual buprenorphine.

Surgical details

The name of the surgeon, the site of the abdominal incision, the operation performed, the time taken for each operation and the volume of blood lost during surgery (estimated by swab weighing) were recorded.

Assessment of pain, sedation and side effects of analgesia after surgery

An assessment of pain and sedation was made at times 1, 3, 6 and 20 h after surgery. Patients completed a horizontal (100-mm) linear analogue scale (LAS) (between "no pain" and "worst pain"). If any patient was unable to mark the LAS, the reason was recorded. They were classified either as patients who experienced "too much pain" (who were regarded as a treatment failure and were given a score of 100 mm on the LAS), or as those who were "too drowsy" (who were regarded as a treatment success and scored zero). A single observer (G.C.P.) assessed the degree of pain using a scale related to movement (Prince Henry Pain Scale (PHPS): 0 = no pain on coughing; 1 = pain on coughing, but not on deep breathing; 2 = pain on deep breathing, but not at rest; 3 = some pain at rest, slight; 4 = pain at rest, severe) (Torda and Pybus, 1984) and sedation with a four-point scale (1 = awake and normal; 2 = drowsy; 3 = sleepy needs to be spoken to; 4 = sound asleep).

Side effects, volunteered by patients, were recorded at each assessment. Each patient and the observer gave an assessment of the efficacy and tolerance (4 = excellent; 3 = good; 2 = acceptable; 1 = poor) of the analgesic treatment at 20 h after surgery.

Respiratory assessments

Following surgery, the ventilation rate, counted over 1 min, was recorded hourly and, if the rate decreased below 8 b.p.m. the infusion of the trial analgesic was discontinued and one of the investigators (G.C.P.) informed.

A blood sample was taken from a radial artery of each patient the day before surgery for blood-gas analysis and repeated at 20 h after surgery for comparison. Each patient was given oxygen ($FI_{O_2} = 0.3$), following surgery, from a low dead-space mask (Hudson). The oxygen was discontinued at least 30 min before the sampling of arterial blood.

Patients were examined for signs of chest infection at 20 h after surgery. The criteria for chest infection were: pyrexia (axillary temperature > 37 °C), frequent cough, expectoration of purulent sputum and any new abnormality detected on auscultation of the lungs. Chest infection was diagnosed if three or all of these features were present.

Statistical analysis

The results are expressed as mean (SD). The two treatment groups were compared by Wilcoxon rank sum tests for quantitative or ordinal measurements and by chi-squared tests for categorized data. Since a significant number of withdrawals occurred, separate comparisons of the treatment groups were performed, for patients who "completed the trial" (per-design) and for patients considered on an "intention to treat basis". The use of both these methods of presentation of the results of a randomized control clinical trial is recommended by Bulpitt (1983).

RESULTS

Although it had been intended to recruit 100 patients, the trial was stopped by the trial monitor after 55 patients (N = 29, B = 26) had been investigated, as nine patients from the nalbuphine group had to be withdrawn because of inadequate pain relief shortly after surgery (mean 2.5 h). No

TABLE I. *Characteristics of patient groups (SD). * Median (interquartile range)*

	Nalbuphine ($n = 29$)	Buprenorphine ($n = 26$)
Sex (male)	15	11
Age (yr)	51 (15)	52 (13)
Weight (kg)	64 (10)	68 (12)
Height (cm)	167 (8)	166 (7)
No. with previous hospital admission	26	24
No. with a previous general anaesthesia	26	23
No. who smoke cigarettes	19	13
No. who consume alcohol	22	17
No. ASA I	6	10
No. ASA II	23	16
Systolic arterial pressure (mm Hg)	129 (18)	125 (14)
Diastolic arterial pressure (mm Hg)	79 (9)	79 (10)
Heart rate (beat min^{-1})	77 (9)	77 (10)
No. with abnormal ECG	5	3
Personality scores		
Psychoticism (max 25)	2 (2)	2 (5)
Extrovertism (max 21)	12 (6)	12 (4)
Neuroticism (max 23)	10 (6)	10 (6)
Lie (max 21)	11 (5)	11 (5)
Anxiety, state-trait (max 160)	73 (17)	76 (19)
Duration of operation (min)	110 (43)	106 (43)
Blood loss (ml)*	95 (55–215)	93 (64–306)
Recovery time (min)	17 (12)	12 (10)

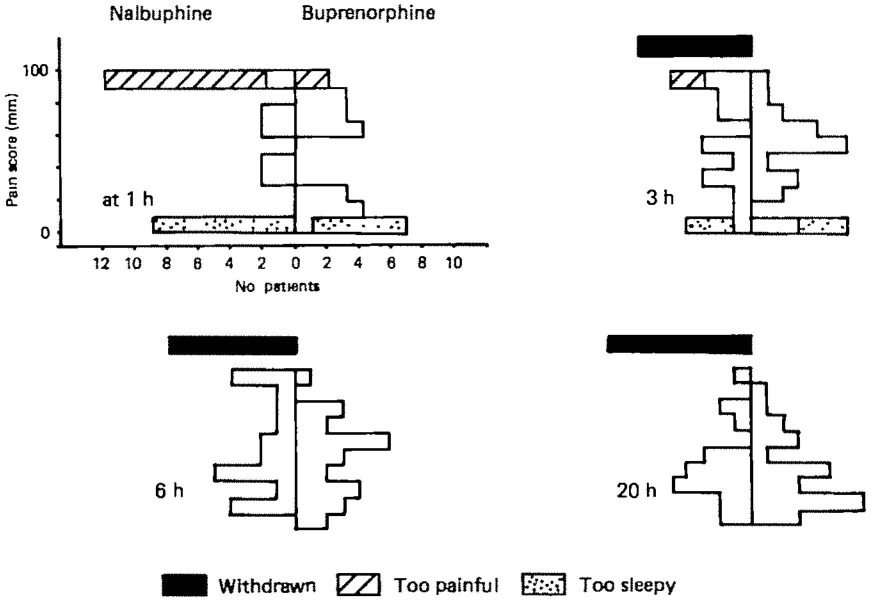

FIG. 1. Comparative distribution of analogue pain scores (LAS) in the two groups at 1, 3, 6 and 20 h after operation.

patient was withdrawn from the buprenorphine group ($P < 0.01$).

Assessments before surgery

The study groups were well matched for the following variables: sex, age, weight, height, number of hospital admissions and previous general anaesthetics, smoking habits, alcohol consumption, ASA physical status, pre-operative arterial pressure, heart rate, ECG abnormalities, and personality traits (psychoticism, extrovertism, neuroticism and lie score) and anxiety (state and trait score) (table I).

Anaesthesia, trial analgesic and surgical details

The two analgesic groups were well matched for the anaesthesic technique and there was no difference with respect to recovery times (table I).

The syringes of nalbuphine had been stored for a shorter mean time than buprenorphine before administration to patients (N = 2.6 (1.8) days, B = 3.1 (2.3) days).

There was no difference between the analgesic groups with respect to the surgeon, site of abdominal incision, the duration of surgery, or the blood loss during surgery (table I).

Assessment of pain, sedation, side effects, efficacy and tolerance of analgesia after surgery

One hour after surgery, 27 patients (N = 19; B = 8) failed to complete the LAS. A greater number of patients in the nalbuphine group were either in too much pain (10) or too sleepy (9) to mark the LAS, compared with those in the buprenorphine group (2 and 6, respectively) (fig. 1).

Patients were withdrawn from the trial if they continued to complain of severe pain and were considered by the observer to be distressed after receiving 6 ml of additional analgesia. Failure to complete the LAS because of pain or LAS score between 90 and 100 was not an indication for withdrawing a patient from the trial, unless additional volumes of analgesia (> 6 ml) gave inadequate pain relief.

Seven patients in the nalbuphine group had to be withdrawn during the second hour after surgery and a further two patients were withdrawn in the following 6.5 h because of inadequate pain relief. Details of the nine patients who were withdrawn are given in table II. If analysis includes those patients who experienced too much pain to mark the LAS and those who were withdrawn because of severe pain (analysis on an "intention to treat" basis), significantly greater

TABLE II. *Details of patients withdrawn from the study*

Age (yr)	Wt (kg)	Ht (cm)	Additional nalbuphine administered (mg) During op.	Recovery	Ward	Withdrawal time (h)	Operation performed
Female							
52	76	163	30	10	80	9.58	Gastrectomy
30	76	163	20	20	70	1.76	R. hemicolectomy
52	51	160	20	40	30	1.86	Cholecystectomy
Male							
74	79	165	20	20	50	1.25	Sig. colectomy
59	53	173	25	5	70	1.93	Gastrectomy
22	60	168	30	30	30	3.16	Vagotomy + pyloroplasty
51	60	175	20	—	60	1.08	R. hemicolectomy
64	65	173	20	50	10	1.00	Cholecystectomy
53	64	173	10	60	10	1.10	Gastrectomy

pain relief was obtained with buprenorphine at each of the four assessment times (table III, fig. 1). In those patients in each group who completed the study ("completed trial" group), greater pain relief (mean LAS) was obtained with buprenorphine at each of the assessments, but the difference was not significant (table III, fig. 1). The pain scores at 20 h showed similar mean values in both groups (N = 39.1; B = 32.1).

The objective pain scores (PHPS) showed that patients who received buprenorphine had significantly greater pain relief at 1 h after surgery (fig. 2). In those patients who completed the study ("completed trial" group) there was no significant difference in the pain score between the groups at 3, 6 and 20 h. However, if the withdrawn patients were included ("intention to treat" group) buprenorphine gave significantly ($P < 0.01$) greater pain relief at 3, 6 and 20 h (table III, fig. 2).

There was no significant difference in the sedation scores with each analgesic (table III). Similarly, there was no significant difference in the side effects volunteered at each assessment between the analgesic treatments, or in the check list of possible analgesic side effects (table III). No serious side effects were reported with either analgesic.

The patients who received buprenorphine had greater subjective and objective efficacy and tolerance scores at 20 h after surgery, but these scores were not significantly greater than those in the nalbuphine group (table III).

Volume of additional analgesia

Those patients in the nalbuphine group who completed the study required a significantly greater mean total volume of analgesic (7 ml) in addition to the constant infusion, compared with those who received buprenorphine (4.4 ml) ($P < 0.01$). The patients who were withdrawn received the greatest mean total volume of additional analgesic (9.3 ml). The mean cumulative volumes of additional analgesic administered during and after surgery are illustrated in figure 3.

Patients withdrawn from the trial

There were no significant differences in any of the preoperative characteristics (table I) between the patients who were withdrawn and those who successfully completed the study.

The patients who failed to achieve adequate pain relief from additional analgesia were observed more frequently. The "rescue analgesia" with morphine appeared to be more effective for pain relief than buprenorphine. However, in one female patient (age 30 yr, table II) "rescue analgesia" with diamorphine 5 mg i.v., morphine 20 mg i.v. and morphine 30 mg i.m. over 5 h was required before satisfactory analgesia was achieved.

The day after surgery, five of the nine patients withdrawn from the study failed to remember the period of severe pain experienced immediately after surgery. On completion of the study for six patients (N = 1, B = 5) the pain-relieving drug had to be changed to morphine (i.m.) because of either nausea or inadequate analgesia with sublingual buprenorphine.

Respiratory assessments

Patients who received nalbuphine had a significantly greater mean lowest ventilatory rate and

TABLE III. *Significance values (P) for buprenorphine compared with nalbuphine, illustrating the differences between the two analgesic treatments, in those patients who completed the trial and those on an "intention to treat" basis. LAS = linear analogue score, PHPS = Prince Henry Pain Scale; ns = not significant. *"Intention to treat" not included as a value could not be assigned in those patients who had been withdrawn*

		Time after surgery (h)			
Assessment	Basis	1	3	6	20
LAS	Completed trial	ns	ns	ns	ns
	Intention to treat	< 0.01	< 0.05	< 0.05	< 0.01
PHPS	Completed trial	< 0.01	ns	ns	ns
	Intention to treat	< 0.01	< 0.01	< 0.01	< 0.01
Sedation	Completed trial	ns	ns	ns	ns
	Intention to treat*	—	—	—	—
Side effects	Completed trial				
	Volunteered	ns	ns	ns	ns
	Check list	ns	ns	ns	ns
	Intention to treat*	—	—	—	—
Efficacy					
Subjective	Completed trial	—	—	—	ns
	Intention to treat	—	—	—	< 0.01
Objective	Completed trial	—	—	—	ns
	Intention to treat	—	—	—	< 0.01
Tolerance					
Subjective	Completed trial	—	—	—	ns
	Intention to treat*	—	—	—	—
Objective	Completed trial	—	—	—	ns
	Intention to treat*	—	—	—	—

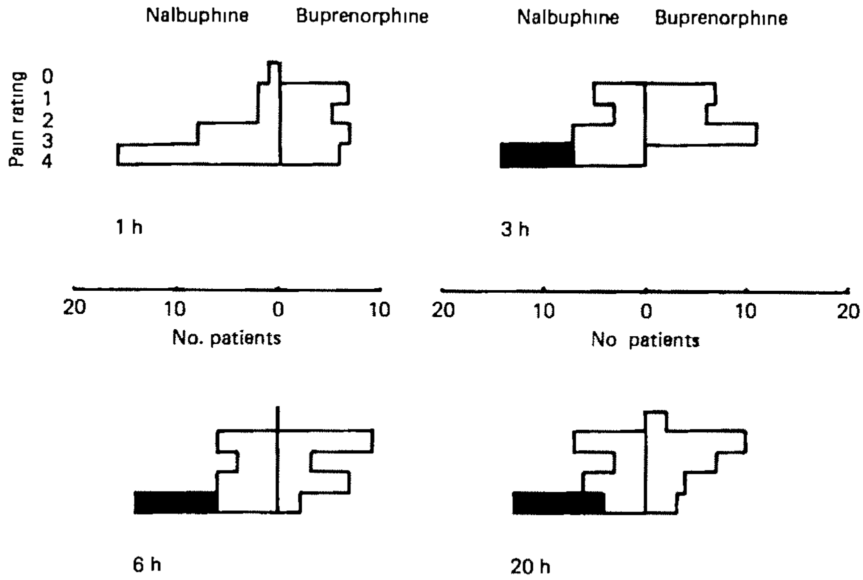

FIG. 2. Comparative distribution of pain rating scores (PHPS) in the two groups at 1, 3, 6 and 20 h after operation.

mean ventilatory rate (table IV). Five patients who received buprenorphine had their analgesic infusion stopped for short periods (1–3 h) because the ventilatory rate had decreased to less than 8 b.p.m. However, no patient required treatment to reverse the depression of ventilatory rate. The

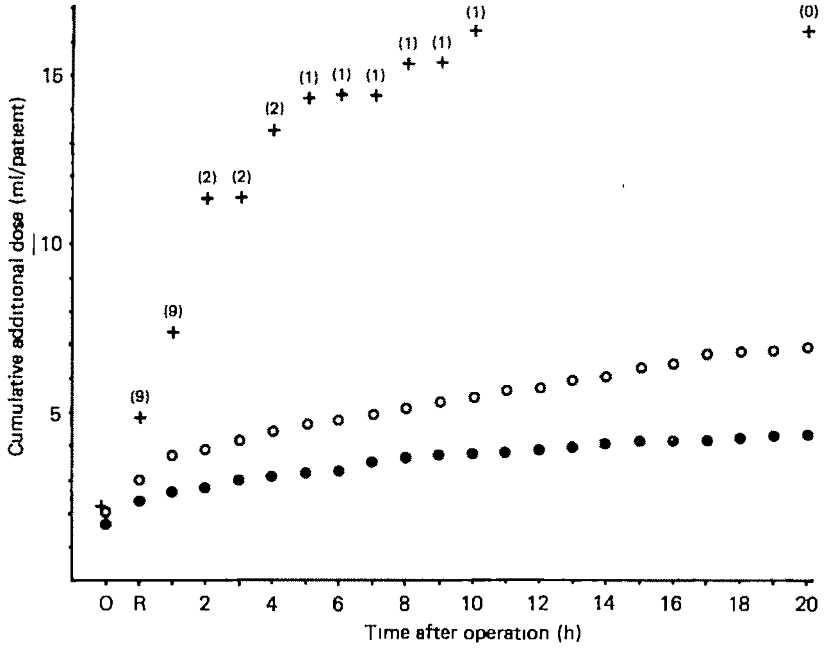

FIG. 3. Mean values of cumulative additional doses of analgesic (ml/patient) during and after operation. (O = During operation; R = in recovery area). ● = Patients receiving buprenorphine; ○ = patients receiving nalbuphine; + = patients receiving nalbuphine who were subsequently withdrawn from the study (the numbers remaining in this group are shown in parentheses).

TABLE IV. *Respiratory assessments (SD)*

	Nalbuphine ($n = 20$)	Buprenorphine ($n = 26$)	P
Mean lowest rate (b.p.m.)	16.4 (4.0)	9.6 (2.7)	< 0.001
Mean rate (b.p.m.)	19.5 (3.4)	13.6 (2.9)	< 0.001
Pa_{O_2} (kPa)			
Before surgery	12.6 (1.5)	12.1 (1.5)	ns
After surgery	9.5 (1.8)	8.4 (1.2)	< 0.05
Mean change	−3.0 (1.6)	−3.7 (1.8)	ns
Pa_{CO_2} (kPa)			
Before surgery	4.7 (0.4)	4.5 (0.4)	ns
After surgery	5.1 (0.5)	5 6 (0.6)	< 0.01
Mean change	0.5 (0.4)	1 1 (0.6)	< 0.001
Chest infection	3 (15%)	10 (38.5%)	ns

change in Pa_{CO_2} after operation was significantly greater with buprenorphine ($P < 0.001$). A greater number of patients who received buprenorphine were diagnosed as having a chest infection (N = 3/20; B = 10/26), but the difference between the groups was not significant (table IV). In those patients who had received buprenorphine, no relationship was found between chest infection and smoking, personality (neuroticism), or site of surgical incision.

Physiotherapy assessment

The two analgesic treatment groups were well matched for all the physiotherapy assessments before surgery (fig. 4). Significantly greater pain relief ($P < 0.05$) and lung expansion ($P < 0.05$)

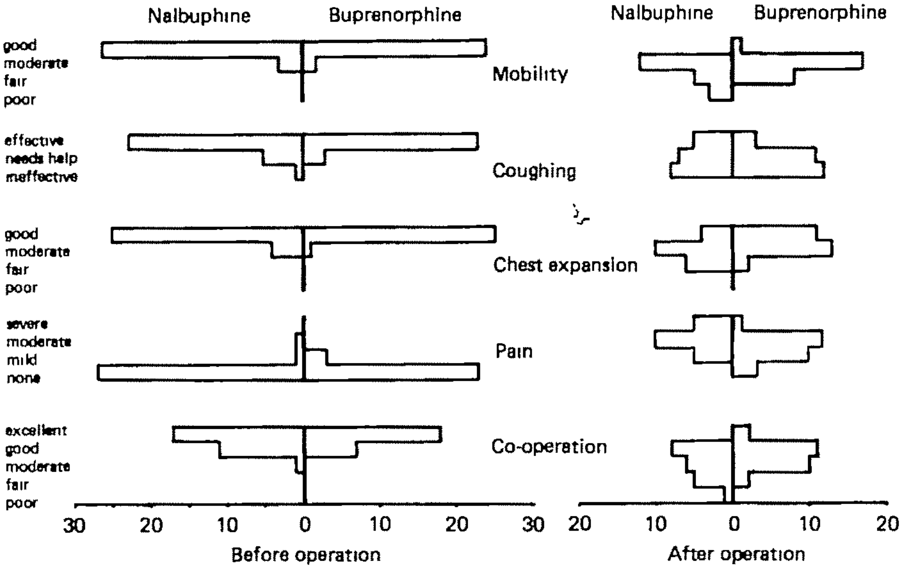

FIG. 4. Comparative distribution of the physiotherapy assessments in the two groups before and at 20 h after operation.

was found after surgery in those patients who received buprenorphine (fig. 4). The increase in pain after operation was significantly less in the buprenorphine group ($P < 0.05$). There was a suggestion that patients in the buprenorphine group had greater mobility and performed better at physiotherapy, but had less effective cough. However, the differences were not significant (fig. 4).

DISCUSSION

Methods

Comparative studies of analgesia are notoriously difficult to perform as they involve the sensory (physical), emotional (cognitive) and evaluative (motivational) aspects of pain (Melzak, 1971), which may be regarded as representing the body, mind and culture (Nayman, 1979). Our study paid particular attention to those variables which possibly had an influence on the patient's response to pain, the selection of equipotent analgesic doses and the assessment of pain relief.

We selected a "data base" of variables which may have had an influence on the patient's response to pain. Taenzer, Melzak and Jeans (1986) have suggested that a patient's anxiety, extroversion, depression, education level, previous chronic pain syndrome and bias towards using medication is a good predictor of postoperative analgesia. The response to analgesia may also depend on the sex of the patient, but the evidence is conflicting (Glynn, Lloyd and Folkard, 1976; Dalhström et al., 1982; Tamsen, Bondessa et al., 1982; Tamsen, Hartvig et al., 1982). Stratification for sex ensures an equal sex distribution in completed drug trials.

The choice of equipotent doses of analgesics in comparative studies is equally important. Few studies have compared the analgesic efficacy of nalbuphine and buprenorphine given as a continuous infusion after surgery. Therefore, the choice of equipotent doses would have to be made from comparison of each drug with morphine (nalbuphine: Beaver and Feise (1978) and Bahar, Rosen and Vickers (1985); buprenorphine: Downing, Leary and White (1977), Tigerstedt and Tammisto (1980) and Bradley (1984)). Although these studies suggested that the nalbuphine:buprenorphine potency ratio should be 33:1, we considered this ratio to be too high, from clinical experience, and decided that a potency ratio of 66:1 would be more appropriate. To compensate for any difference in potency, each patient had the oportunity of achieving the same level of pain relief because additional analgesia could be given on request. Therefore, any difference in pain relief which occurred between the groups was unlikely to be the result of an incorrect assessment of relative potency and would more likely be the result of a difference in analgesic efficacy. The total dose of nalbuphine administered by continuous infusion in this study was greater than that recommended (data sheet) for intermittent treatment of severe pain by the i.m. route, over a similar period of time. To allow direct comparison with nalbuphine, buprenorphine was administered i.v., rather than sublingually as recommended.

A single assessment of pain at 24 h after surgery has been criticized as inaccurate (Smith, 1985), so objective and subjective assessments of the degree of pain were made frequently after surgery in this study. The LAS seems the best subjective method of assessing pain relief in patients after surgery (Revill et al., 1976), but has the disadvantage that some patients may be unable to perform the assessments shortly after surgery. More than 50% of our patients who received nalbuphine were unable to complete the LAS 1 h after surgery because of either severe pain or sedation. This contrasts with the study of Kay and Krishnan (1986) who administered nalbuphine by the patient-controlled method for 4 h after abdominal surgery. They found that all their patients completed the LAS each hour or until they were withdrawn from the study. This is surprising since they reported that "a number of patients were unable to operate the palliator at sometime during the trial and requested help from nursing or medical staff to obtain another dose". We attempted to categorize our patients as a treatment "success" or "failure", depending on the reason for the failure to mark the LAS. At the last assessment, the pain scores for both analgesics were approximately normally distributed, with a mean score similar to that recorded for other analgesic studies (Vickers, 1985).

Bahar and colleagues (1985) suggested that pain during movement may be a useful discriminator between analgesic drugs. Therefore, a physiotherapy assessment and a scale relating pain to movement (PHPS) was used in the present study for the objective assessments of pain.

Assessments of sedation made by the observer were considered to be more accurate than subjective assessments, because patients did not have to be aroused.

Analgesic efficacy

Potency relates to the dose of a drug required to produce a given effect, whereas efficacy relates to the maximum effect that a drug is capable of producing. We attempted to compensate for any differences in potency between the nalbuphine and buprenorphine by allowing patients the opportunity of reaching the same level of analgesia. We chose a nalbuphine: buprenorphine potency ratio of 66:1 and found that the ratio of the total dose of each analgesic administered to those patients who completed the trial was 75:1. The trial was discontinued when a significant number of patients had to be withdrawn because of inadequate pain relief with nalbuphine. This suggests that either the analgesic efficacy of nalbuphine is less than that of buprenorphine, or nalbuphine analgesia is antagonized at higher doses (Welch and Feldman, 1981). Our results indicate that patients who fail to gain adequate analgesia from small doses of nalbuphine may not achieve greater pain relief with additional doses. Kay and Krishnan (1986) suggested that, in patients after abdominal surgery, a maximum degree of analgesia was obtained with nalbuphine 0.3–0.5 mg kg^{-1}. The present study suggests that the E′a max (Effect maximum for analgesic efficacy) for nalbuphine represents a mean total cumulative dose of 0.84 mg kg^{-1} at 2.5 h or 2.7 mg kg^{-1} at 20 h after surgery. The E′a max may follow the E′rd max (Effect maximum for respiratory depression) (Romagnoli and Keats, 1980; Gal, DiFazio and Moscicki, 1982).

The lack of analgesic efficacy of nalbuphine in the present study contrasts with the results of Tammisto and Tigerstedt (1977), Beaver and Feise (1978) and Bahar, Rosen and Vickers (1985). What are the possible reasons for this difference? The mechanism of action of nalbuphine at the receptor level is unclear, but may involve more than one opioid receptor (Jasinski, 1984). Studies which assess the effectiveness of agonist/antagonist analgesics should be confined to the analgesic under study, because interpreting the results is difficult when other opioids ("second opioids") have been given, as they may contribute to the relief of pain. Tammisto and Tigerstedt (1977), in a study that compared the effectiveness of nalbuphine and pentazocine for pain relief in patients 4 h after abdominal surgery, premedicated their patients with pethidine. Similarly, in a study to compare the effectiveness of self-administered nalbuphine, pethidine or morphine for pain relief, Bahar, Rosen and Vickers (1985) gave patients fentanyl during anaesthesia for cholecystectomy and assessed pain relief 3 h after surgery. In these studies the analgesia contributed by the second opioid may have been significant in the first few hours after surgery. Beaver and Feise (1978) compared nalbuphine and morphine in patients at 24 h after surgery. Before this, they administered their "unual analgesic" but they did not report the analgesic, the number of doses, or the timing of the doses.

"Acceptable relief of pain" has been reported with nalbuphine in patients following cholecystectomy (Vatashsky and Haskel, 1986), but this study was open, with no formal testing of pain relief and no comparison group. Lehmann and Tenbuhs (1986) have reported good efficacy and patient acceptance in an open, uncontrolled study with nalbuphine. However, their patients received fentanyl and droperidol, or pethidine or triflupromazine, as premedication and fentanyl and diazepam during surgery. Assessments were made retrospectively the day after surgery.

Amnesia

Amnesia has been reported by Kay and Krishnan (1986) in patients receiving large doses of nalbuphine. In the present study, more than 50% of the patients who were withdrawn from the trial because of inadequate analgesia, failed to remember the period of severe pain following surgery when interviewed at 20 h after operation. We have made this observation previously, in a dose–response study with nalbuphine, in patients having upper abdominal incisions (Pugh and Drummond, 1987). The amnesia could be the effect of nalbuphine or possibly the result of subsequent "rescue analgesia". Amnesia for pain in the early postoperative period reinforces the recommendation for regular assessments of pain relief after surgery (Smith, 1985).

Ventilatory assessments

This study confirmed that nalbuphine, even in large doses, failed to depress the ventilatory rate (Vatashsky and Haskel, 1986). Patients who received buprenorphine had a significantly lower ventilatory rate (Tigerstedt and Tammisto, 1980; Fry, 1982) with a greater increase in Pa_{CO_2} after operation. Clinically it seems that patients who have a slower ventilatory rate after operation have better pain relief. This maxim is supported by our results.

Physiotherapy assessment

Good analgesia may be important to allow coughing and effective sputum clearance, possibly preventing the development of atelectasis. Few studies on the efficacy of analgesia after surgery have reported an assessment by a physiotherapist. In this study, the physiotherapist was able to detect a significant difference between the analgesics when the observer was unable to do so. In future studies an assessment by a physiotherapist may be useful to discriminate between analgesics. Our results support the view of Bahar, Rosen and Vickers (1985), who suggested that an assessment which relates pain to movement is a good discriminator between analgesics.

CONCLUSIONS

The present study suggests that nalbuphine, as the sole analgesic, is inappropriate for patients after abdominal surgery. Some patients may obtain adequate analgesia from relatively small doses of nalbuphine. However, if a small dose of nalbuphine is insufficient, further analgesia from a larger dose may not be achieved. It is not possible to predict which patient is likely to respond. Nalbuphine appears to have a low E′a max and analgesia may be antagonized at the higher dose. The study confirmed the effectiveness of buprenorphine for pain relief after abdominal surgery.

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GENERAL ANAESTHESIA IN MOTHERS WITH SEVERE PRE-ECLAMPSIA/ECLAMPSIA

H. CONNELL, J. G. DALGLEISH AND J. W. DOWNING

SUMMARY

Twenty patients with severe pregnancy induced (PIH) or pregnancy aggravated (PAH) hypertension, undergoing general anaesthesia for Caesarean section were studied. All patients received a standard anaesthetic technique designed to control the potentially dangerous, reflex cardiovascular instability associated with laryngoscopy. The average increase in systolic arterial pressure (SAP) was 56.4 mm Hg following laryngoscopy and tracheal intubation.

Arterial hypertension and tachycardia are demonstrable in most patients as a response to laryngoscopy and intubation (King et al., 1951; Takeshima, Noda and Higaki, 1964). The reflex, which is mediated by sympathetic and sympathoadrenal activity (Derbyshire and Smith, 1984), is even more pronounced in the hypertensive patient (Prys-Roberts, Meloche and Foëx, 1971).

This exaggerated response to airway manipulation is a cause for particular concern in patients with pregnancy induced (PIH) or pregnancy aggravated (PAH) hypertension, since the commonest causes of death in pre-eclampsia are cerebral haemorrhage (30–40 %) and cerebral oedema (18–20 %), whilst one survey showed that 78 % of patients suffered from cardiac hypertrophy at postmortem (Hibbard, 1973; Lopez-Llera, Linares and Horta, 1976; Wright, 1983). Indeed, overt cardiac failure has been reported in association with PAH as a direct result of tracheal intubation (Fox et al., 1977). These considerations emphasize the importance of using an anaesthetic technique capable of minimizing cardiovascular instability.

PATIENTS AND METHODS

Twenty patients with severe PIH or PAH (admission diastolic arterial pressure > 110 mm Hg) undergoing Caesarean section, were studied. Routine monitoring included measurement of central venous pressure and intra-arterial pressure.

Control values of systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressure, and of heart rate were recorded before the induction of anaesthesia. Hypertension (SAP > 170 mm Hg) was controlled with an infusion of 0.125 % trimetaphan and tachycardia (> 100 beat min^{-1}) with practolol 2 mg i.v. repeated until the heart rate decreased by 10 % or a maximum dose of 0.2 mg kg^{-1} had been administered.

Patients were pre-oxygenated for 3–5 min and received domperidone 10 mg and lignocaine 1 mg kg^{-1} i.v., then anaesthesia was induced using a rapid sequence induction consisting of etomidate 0.2 mg mg^{-1}, cricoid pressure and suxamethonium 100 mg.

Following intubation of the trachea, ventilation of the lungs was continued mechanically using a Manley ventilator delivering 8–10 litre min^{-1} of a mixture of 50 % nitrous oxide in oxygen supplemented with 0.5 % halothane. Muscle paralysis was maintained using alcuronium 0.2 mg kg^{-1} except in patients who had received magnesium sulphate in the preoperative period, in whom the dose was reduced to 0.1 mg kg^{-1} since magnesium ions potentiate neuromuscular blockade (Ghoneim and Long, 1970).

H. CONNELL, M.B., CH.B., F.F.A.R.C.S., Sir Humphry Davy Department of Anaesthesia, Bristol Royal Infirmary, Bristol BS2 8HW. J. G. DALGLEISH, B.SC., M.B., B.S., F.F.A.R.C.S., Department of Anaesthesia, St Richards Hospital, Chichester PO19 5SE. J. W. DOWNING,* M.B., B.CH., F.F.A.(S.A.), F.F.A.R.C.S., Department of Anaesthesia, University of Natal, Box 17039, Congella 4013, Republic of South Africa.
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*Present address: University Department of Anaesthesia, Queens Medical Centre, University of Nottingham, Nottingham.

TABLE I. *Patient demographic data, preoperative anti-hypertensive therapy, infant weight, Apgar score (A–C) and post-intubation increase in SAP. *Patient subsequently died. NR = Not recorded; IUD = intra-uterine death*

Patient No.	Age (yr)	Parity	Albuminuria	SAP/DAP on admission (mmHg)	Dihydrallazine (mg)	SAP inc. after intubation (mm Hg)	Witnessed convulsions	Apgar (A–C) 2 min	Apgar (A–C) 5 min	Birth wt (kg)	Comments
1	39	2^{+3}	2^{+}	160–190 120	6.25	100		8	8	2.13	Diazepam 10 mg i.v. Previous LSCS
2	20	0^{+1}	3^{+}	180 120	6.25	25	×3	IUD	—	1.81	Diazepam 10 mg i.v. Comatose → ITU
3	27	0^{+1}	NR	160–190 120	12.5	110		6	8	1.34	Na Guardinal 200 mg
4	20	0^{+1}	2^{+}	170–190 110	6.25	20		8	8	3.70	
5	16	0^{+1}	3^{+}	150–180 100–110	12.5	55	×3	6	8	2.45	Diazepam 10 mg i.m.
6	16	0^{+1}	NR	230 130		35	×2	6	8	2.85	Diazepam 10 mg i.v.
7	22	1^{+2}	NR	170–180 100–110	12.5	75	×2	1	3	1.87	Diazepam 10 mg i.v. Comatose → ITU Dexamethazone 32 mg
8	28	4^{+5}	3^{+}	180–200 110–130		90		6 4	8 7	2.65 3.75	Twins
9	16	0^{+1}	NR	170–190 120–130	12.5	45	×3	4	8	2.56	Diazepam 10 mg i.v.
10	22	0^{+1}	3^{+}	170–190 120–130		45		2	8	1.78	
11	38	8^{+9}	2^{+}	180–210 100–120	6.25	70		8	8	4.80	Na Guardinal 200 mg Aldomet 250 mg daily
12	25	2^{+3}	NR	190–210 120–140	6.25	35		6	7	1.65	
13	35	4^{+5}	3^{+}	240–250 140–150	25	75	×1	6	3	1.38	Comatose → ITU* Dexamethazone 32 mg
14	27	0^{+1}	NR	180–210 105–120		45		8	7	2.65	Na Guardinal 200 mg
15	22	0^{+1}	2^{+}	170–180 110–120		45		2	6	1.22	A. P. H. Aldomet 250 mg twice daily Na Guardinal 200 mg
16	24	0^{+1}	NR	155–170 110–120		30	×1	8 7	8 6	1.90 1.85	Twins
17	16	0^{+1}	3^{+}	160–175 105–115		25	×2	3	6	1.86	
18	17	0^{+1}	NR	160–180 105–120		50		1	4	2.65	
19	19	0^{+1}	3^{+}	180–200 115–125		45	×2	6 1	8 3	1.75 1.35	Twins Diazepam 10 mg i.v.
20	23	4^{+5}	3^{+}	230–240 120–140	12.5	110	×2	2	5	0.55	Comatose → ITU* Dexamethazone 32 mg 20% Mannitol 200 ml

After the delivery of the infant, papaveretum 10–20 mg was injected i.v. and an infusion of Syntocinon 20 iu in 750–1000 ml of plasmalyte solution was commenced. At the termination of surgery the residual effects of alcuronium were antagonized by the i.v. administration of neostigmine 2.5 mg, and glycopyrrolate 0.6 mg, except in eclamptic patients who were transferred directly to the intensive care unit on IPPV as part of their management.

Induction to delivery (I–D) intervals, uterine incision to delivery (U–D) intervals and time to sustained neonatal respiration (TSR) were noted. A clinical assessment of fetal status using the Apgar score modified to exclude colour (A – C) was made at 2 min and 5 min after birth (Crawford, Davies and Pearson, 1973).

Since we were anticipating a non-uniform cardiovascular response to larynoscopy and intubation in this group of mothers, we decided to study the patients in two groups. Those manifesting a less severe response (arbitrarily defined as an increase in SAP < 60 mm Hg) were designated as group 1 and those showing a more severe response (increase in SAP > 60 mm Hg), group 2.

Statistical analyses of the data were performed using the Mann–Whitney *U* test, a ranking test designed to compare groups of unequal sizes, and *z* values were derived using standard formulae. A probability value of $P < 0.05$ was considered statistically significant.

RESULTS

Pre-anaesthetic patient data, including previous antihypertensive therapy are summarized in table I.

The mean age of the patients studied was 23.6 yr, with an average parity of 1.25. When the patient first entered the operating room, average arterial pressures were SAP 168 mm Hg, MAP 134 mm Hg and DAP 112 mm Hg.

The mean (±SEM) SAP, DAP and MAP recorded during the induction of anaesthesia and up to 5 min after delivery are presented in figure 1, and show that the average increase in SAP following laryngoscopy and intubation was 56.4 mm Hg.

Six patients received trimetaphan only in addition to the standard induction agents. A further six were given trimetaphan and practolol, and six received practolol alone. Thus, 12 patients received β-adrenergic blockers; two required no drugs other than those included in the standard anaesthetic induction sequence.

The heart rate response to the induction of anaesthesia can be seen in table II; there was a significantly greater increase in heart rate in those

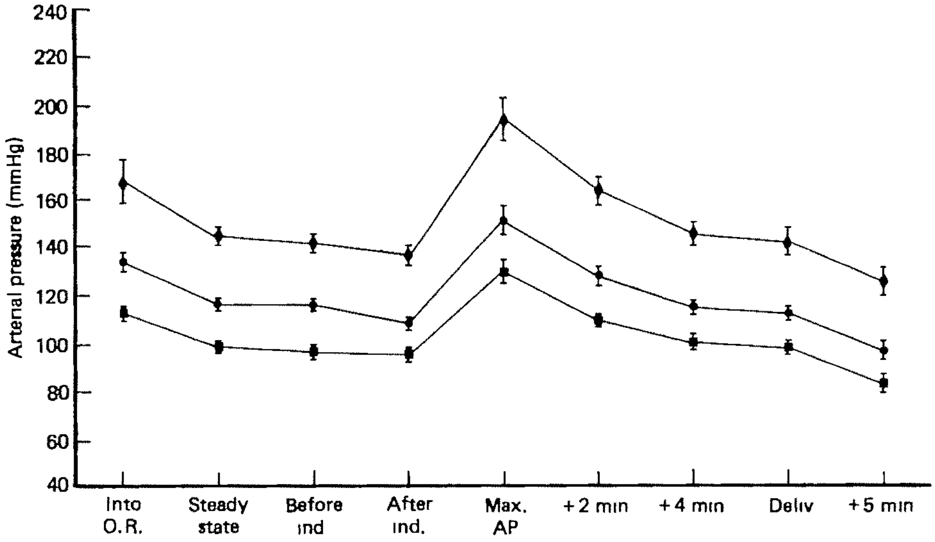

FIG. 1. Haemodynamic responses: SAP (◆), MAP (●) and DAP (■) (mean ± SEM) in total study group ($n = 20$) from time of entering operating room to 5 min after delivery of infant.

patients who did not receive a β-blocker (30.3% v. 11.3%, $P < 0.01$).

There were two maternal deaths in this group of patients. Both patients were deeply unconscious upon admission (responding only to painful stimuli). One had a right hemiplegia before anaesthesia was induced and the other was shown subsequently on CAT scan to have suffered a pontine haemorrhage at an unspecified time.

TABLE II. *Effect of β-blockade on the heart rate (HR) response to laryngoscopy and intubation.* *P < 0.01

	β-blocker		No β-blocker
HR (beat min^{-1})			
Initial	117		86
After treatment	99		—
After intubation	110		111
Increase (%)	11.3%	*	30.3%

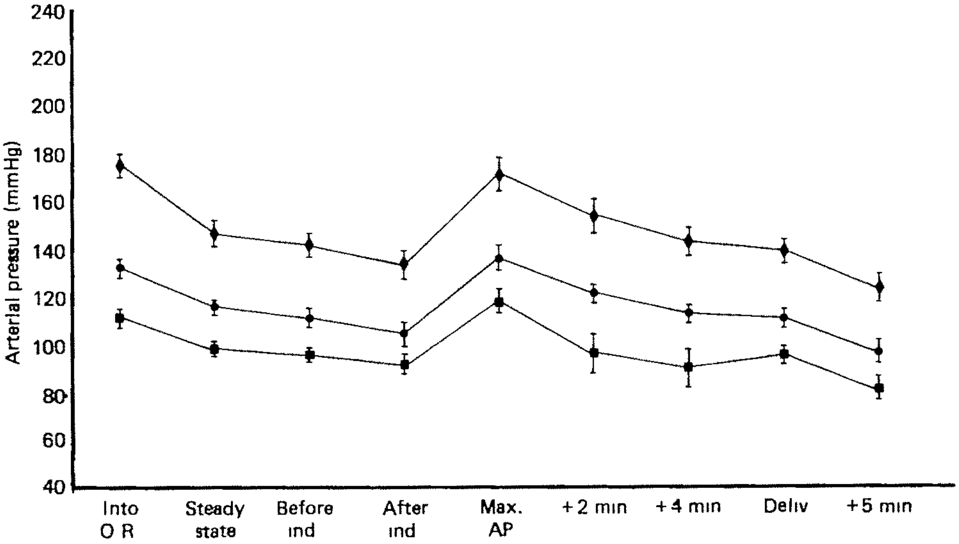

FIG. 2. Haemodynamic responses: SAP (◆), MAP (●) and DAP (■) (mean ± SEM) for group 1 ($n = 13$) from time of entering the operating room to 5 min after delivery of the infant.

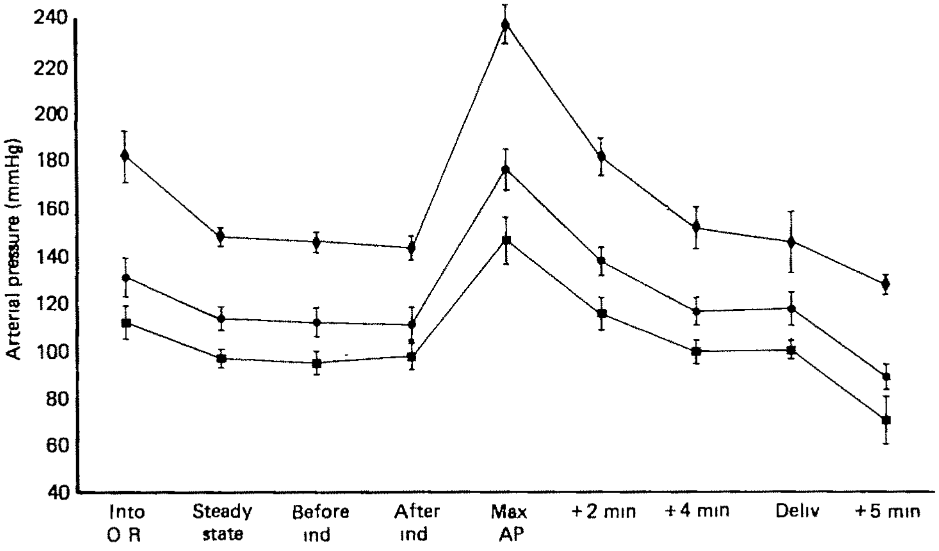

FIG. 3. Haemodynamic responses SAP (◆), MAP (●) and DAP (■) (mean ± SEM) for group 2 ($n = 7$) from time of entering the operating room to 5 min after delivery of infant.

TABLE III. *Patient data and haemodynamic response to standard anaesthetic technique in groups 1 and 2*

	Group 1	Group 2	*P*
No. of patients	13	7	
Age (yr)	20.0	30.3	0.0013
Parity	0.15	3.29	0.0071
Mean increase in MAP (mm Hg)	30.9	65.3	
Mean increase in SAP (mm Hg)	38.5	90.0	
No. eclamptic patients	7	3	
No. comatose	1	3	
Maternal deaths	0	2	

Twenty-two live infants were delivered, there being three sets of twins. One infant was stillborn and one (birth weight 550 g) died within 24 h of delivery. In neither case was anaesthesia thought to be a contributory factor. Individual modified Apgar scores (A – C) at 2 and 5 min, together with birth weights of infants, appear in table I. The mean time to sustained spontaneous neonatal respiration was 90.4 s. The latter figure excludes four infants who were severely affected and failed to breathe. Their tracheae were, therefore, intubated and ventilated and the infants transferred to the special care neonatal unit.

There were 13 patients in group 1 (SAP increase < 60 mm Hg) and seven (group 2) who showed more marked changes in arterial pressure (> 60 mm Hg). Although the average increase in SAP in the whole series was 56.4 mm Hg, in group 1 this figure was 38.5 mm Hg, compared with an increase of 90.0 mm Hg in group 2 ($P < 0.05$). These differences are detailed in figures 2 and 3 and in table III.

DISCUSSION

The choice of trimetaphan to decrease arterial pressure was based on two considerations: first, its effect upon intracranial pressure is more benign than that of either sodium nitroprusside (Turner et al., 1977) or nitroglycerine (Writer et al., 1980) and, second, the theoretical possibility of fetal cyanide poisoning consequent upon the metabolic breakdown of sodium nitroprusside (Naulty, Cefalo and Lewis, 1981). It must be emphasized, however, that both have been used effectively and safely in non-hypertensive pregnant patients (Rigg and McDonagh, 1981; Hood, Dewan and James, 1983).

Practolol (mean dose 0.1 mg kg^{-1}) was administered to patients whose heart rates exceeded 100 beat min^{-1} before the induction of anaesthesia because it has been suggested that the prior administration of a specific β-adrenergic blocking agent is effective in ameliorating reflex cardiovascular changes in hypertensive patients (Prys-Roberts et al., 1973). We used a smaller dose (0.1 *v.* 0.4 mg kg^{-1}) than Prys-Roberts in his group of controlled hypertensive subjects, since all our patients required emergency anaesthesia, and in only a small number could the hypertension be said to have been controlled before the patient entered the operating room. Despite encouraging evidence in animals and man (Berk et al., 1967; Berk et al., 1972) as to the protective effects of β-blockade against haemorrhagic shock, we were reluctant to administer a higher dose in a potentially volume-depleted group of patients, who could be expected to be less tolerant of haemorrhagic hypovolaemia.

An i.v. injection of lignocaine 1 mg kg^{-1} also preceded rapid sequence induction. This practice is routine in the neurosurgical anaesthetic department in Durban, since it has been shown not only to control haemodynamic changes induced by tracheal intubation (Denlinger et al., 1976), but also to prevent intracranial hypertension secondary to airway manipulation (Donegan and Bedford, 1980).

Both increasing age and parity have been identified as significant prognostic indicators of maternal mortality (Lopez-Llera, Linares and Horta, 1976; Moodley, Naicker and Mankowitz, 1983) and when we compared our less severely affected group of patients (group 1) with the more severely affected group 2, there were significant differences between the two groups in terms of age ($P < 0.005$) and parity ($P < 0.01$). Most patients (12/13) in group 1, were primigravid of mean age 20.0 yr, contrasting with the average age in group 2, which was 30.3 yr, in what was generally a multiparous cohort (mean parity 3.3). Despite the higher incidence of pre-eclampsia/eclampsia in young primiparous patients, the majority of deaths occur in the more elderly (mean age 27.5 yr) parous mothers. We would, therefore, expect a more favourable outcome in the younger patients comprising group 1, and this seemed to be the case. There were no maternal deaths in primigravid patients younger than 27 years old and their haemodynamic responses were less extreme (mean post-laryngoscopy increase in

SAP 38.2 mm Hg *v.* 78.9 mm Hg) than in the other patients ($P < 0.01$).

Three of the four deeply comatose patients, two of whom subsequently died, fell into the category manifesting a change in SAP > 70 mm Hg. This again confirms that impaired consciousness is an important risk factor (Moodley, Naicker and Mankowitz, 1983).

Modified Apgar scores showed there to be nine severely affected infants ($A - C < 5/8$) at 2 min and five such infants after 5 min, suggesting that the infants delivered constituted a severely compromised group, in keeping with the hostile intra-uterine environment.

Since the object of this study was to find a safe general anaesthetic technique applicable to all mothers presenting with severe pre-eclampsia/eclampsia, we failed in our objective. However, we believe this technique to be satisfactory and safe for young primiparous mothers who do not display signs of impaired consciousness. We confirm that increasing age and parity, as well as an obtunded conscious level constitute special hazards in hypertensive obstetric patients, demanding perhaps a quite different approach. In these patients we believe the safest way of obtunding the hypertensive response to rapid sequence induction would be to use a potent synthetic opioid such as fentanyl or alfentanil (Cork et al., 1984), provided that a good perinatal service exists for treatment of the affected infant after delivery. This approach seems worthy of serious consideration in the light of the major risk to maternal and fetal wellbeing presented by exacerbation of maternal hypertension during emergency anaesthetic induction of the severe pre-ecalamptic/eclamptic patient.

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FENTANYL–DROPERIDOL SUPPLEMENTATION OF RAPID SEQUENCE INDUCTION IN THE PRESENCE OF SEVERE PREGNANCY-INDUCED AND PREGNANCY-AGGRAVATED HYPERTENSION

E. G. LAWES, J. W. DOWNING, P. W. DUNCAN, B. BLAND, N. LAVIES AND G. A. C. GANE

SUMMARY

Twenty-six patients manifesting severe pregnancy-induced (PIH) or pregnancy-aggravated (PAH) hypertension who presented for emergency Caesarean section under general anaesthesia were studied. All patients came from a previously identified high risk group—namely > 25 yr, multiparous and with diastolic arterial pressures sustained at > 120 mm Hg. Our standard accelerated induction technique for the management of severely hypertensive mothers was modified to include the use of fentanyl and droperidol before induction. This modification of the induction sequence produced a clinically significant amelioration of the reflex sympathetic hypertensive response to laryngoscopy and intubation in most mothers receiving antihypertensive therapy, without apparent deleterious effect in the immediate postoperative period to those neonates unaffected by intrauterine asphyxia.

Severe pregnancy-induced (PIH) and pregnancy-aggravated (PAH) hypertension are not infrequently encountered by the obstetric anaesthetist. Patients presenting with either of these conditions represent 5–12% of all deliveries, and 50% of these require delivery by Caesarean section (Moodley, Naicker and Mankowitz, 1983; Crowhurst and Rosen, 1984). In the United Kingdom, pre-eclampsia/eclampsia was previously the third most common cause of maternal mortality (Hibbard and Rosen, 1977; DHSS, 1982). In the triennium 1979–81, hypertensive diseases of pregnancy were the most frequent causes of death reported in the Confidential Enquiry in Maternal Mortality. Four of the deaths associated with anaesthesia occurred in mothers suffering from pre-eclampsia (DHSS, 1986). This problem would appear to be increasing in developing countries (Rosenfield and Maine, 1985).

In the absence of fetal distress or other specific contraindication, extradural anaesthesia will control the arterial pressure and provide surgical anaesthesia without serious disadvantage to mother or fetus (Moir, Victor-Rodrigues and Willcocks, 1972; Gutsche, 1979). However, further deterioration in the condition of the mother resulting in fetal distress, maternal coagulation problems or maternal convulsions (eclampsia) precludes extradural anaesthesia for emergency Caesarean section. Under these circumstances, general anaesthesia is the only alternative (Gutsche, 1979; Crowhurst and Rosen, 1984). General anaesthesia is not without risk to mother and fetus, since no entirely satisfactory general anaesthetic technique has yet been devised for these severely hypertensive mothers (Gutsche, 1979; Wheeler and Harris, 1982; Marx and Bassell, 1984; Downing, 1984).

Large fluctuations in arterial pressure accom-

E. G. LAWES,* M.B., B.S., F.F.A.R.C.S; J. W. DOWNING,† M.B., B.CH., (WITS) F.F.A. (S.A.), F.F.A.R.C.S. (ENG.); P. W. DUNCAN, M.B., B.CH., F.F.A.R.C.S.; B. BLAND, L.R.C.P., F.F.A.R.C.S.; N. LAVIES, M.B., B.CH., F.F.A.R.C.S.; G. A. C. GANE, B.A., M.B., B.CH., Department of Anaesthetics, University of Natal, Faculty of Medicine, Medical School, P.O. Box 17039, Congella, Durban, Natal, R.S.A. Accepted for Publication: March 30, 1987.

Present addresses: *Shackleton Department of Anaesthetics, Level E, Centre Block, Southampton General Hospital, Southampton SO9 4XY.

†University Department of Anaesthesia, Queens Medical Centre, University of Nottingham, Nottingham.

pany the induction of general anaesthesia for Caesarean section in severely hypertensive parturients (Hodgkinson, Hinsain and Hayashi, 1980; Connell, Dalgleish and Downing, 1987). As with all untreated hypertensive patients, laryngoscopy and intubation are usually associated with an exaggerated pressor response (Prys-Roberts et al., 1971; Prys-Roberts, 1984). These changes in arterial pressure may be mediated by an increase in circulating noradrenaline concentration (Low et al., 1986). Marked increases in systemic arterial, pulmonary arterial and intracranial pressures have been associated with increased morbidity and mortality in both mother and fetus (Fox et al., 1977).

The use of fentanyl and droperidol during the induction of anaesthesia is associated with notable cardiovascular stability (Prys-Roberts et al., 1971; Stoelting et al., 1975). These agents have been used to suppress the cardiovascular response to laryngoscopy and intubation by inhibiting catecholamine release (Russell et al., 1981; Dahlgren and Messeter, 1981; Kautto, 1982; Cork et al., 1984; Black, Kay and Healy, 1984). The aim of this study was to determine if these agents could be used to advantage in the special circumstance of hypertension and pregnancy, in conjunction with standard preoperative antihypertensive regimens. The effect on changes in maternal arterial pressure and the influence on neonatal outcome are reported.

PATIENTS AND METHODS

The study was undertaken with the approval of the Ethical Sub-Committee of the Faculty of Medicine, University of Natal, the Natal Provincial Administration and the Medicines Control Council of South Africa. Twenty-six patients, referred to this unit from outlying hospitals were studied. All patients were older than 25 years of age, multiparous, with sustained diastolic arterial pressures of > 120 mm Hg, and had significant proteinuria.

Once the diagnosis of PIH or PAH was made, a central venous catheter and a radial artery cannula were inserted under local anaesthesia. Direct pressure measurements were recorded on an HP 78304A monitoring system with hard copy facilities. The electrocardiogram was monitored continuously. A 14-gauge peripheral venous cannula was inserted percutaneously (local anaesthesia) and a balanced salt solution (Hartmann's solution) administered to maintain a central venous pressure of 6–8 mm Hg. Antihypertensive therapy initiated by the referring hospital was continued, or started, as appropriate. No attempt was made before admission to this unit to influence the choice of antihypertensive drugs used by the referral hospitals. Base line measurements of acid–base and blood-gas variables were obtained whilst permanent recordings of pretreatment arterial pressure were made.

Preoperative preparation before induction of anaesthesia was determined by the following programme. If conscious, patients were given 30 ml of sodium citrate 0.3 mol litre^{-1} to drink. The patient lay on a wedge (minimum 15°). Fentanyl 100 µg was injected i.v. and 100% oxygen administered by mask. Droperidol 5 mg was injected and a 5-min period elapsed before a further injection of fentanyl 100 µg i.v. Throughout this sequence the upper airway of any comatose patient was protected from aspiration by the application of cricoid pressure. The level of consciousness was otherwise continually monitored by eliciting responses to verbal questioning.

Following the use of i.v. fentanyl and droperidol, systolic arterial pressures (SAP) of > 170 mm Hg or mean arterial pressures (MAP) of > 130 mm Hg were treated by the i.v. administration of bolus doses of trimetaphan 2.5 mg. Induction of anaesthesia commenced only after the successful reduction of pressures (SAP or MAP) to less than these values. Lignocaine 1 mg kg^{-1}, followed by etomidate 0.3 mg kg^{-1} and suxamethonium 1.5 mg kg^{-1} were then given in rapid sequence with cricoid pressure applied. The airway was secured with a cuffed tracheal tube. Maintenance of anaesthesia was achieved with either 0.5% halothane or 0.8% enflurane and 50% nitrous oxide in oxygen. Variations in arterial pressure which occurred following induction and intubation were controlled, if necessary, by manipulating the infusion rate of a 0.1% solution of trimetaphan, using an automatic infusion apparatus. Neuromuscular blockade was maintained with alcuronium 100–120 µg kg^{-1}; patients given magnesium sulphate in the preoperative period received the lower dose of alcuronium (Ghoneim and Long, 1970). The remainder of the anaesthetic was conducted in a standard manner, including the use of Syntocinon i.v. Glycopyrrolate and neostigmine were used to antagonize neuromuscular blockade at the end of the procedure.

Extubation of the trachea in the conscious patient was performed after i.v. trimetaphan had been given in bolus doses of 2.5 mg to reduce SAP to < 170 mm Hg. Throughout the procedure, commencing from initial referral to the unit, permanent beat-to-beat records of arterial pressure were obtained directly from the arterial monitoring line.

Samples of maternal arterial blood taken immediately before delivery and neonatal blood samples obtained from a double-clamped segment of umbilical cord were analysed immediately by an automatic blood-gas analyser (Corning 170 pH/blood-gas analyser).

All neonates were examined immediately after delivery by medical staff experienced in neonatal resuscitation. Assessments of the time to sustained respiration measured in seconds, and a modified Apgar (minus colour) score (0–8) were obtained at 1 and 5 min. Neonates needing resuscitation were given neonatal naloxone 0.04 mg in divided doses by one of three routes: i.m., i.v. or via the tracheal tube. Regardless of their clinical condition following initial assessment, all neonates were transferred to the neonatal intensive care ward.

The recordings of maternal arterial pressure were reviewed and arterial pressures associated with the following events noted: (I) maximum pressure before entering the operating theatre; (II) before fentanyl–droperidol i.v.; (III) 5 min after fentanyl–droperidol i.v.; (IV) immediately before induction; (V) immediately following i.v. lignocaine, etomidate or suxamethonium injections, but before laryngoscopy and tracheal intubation; (VI) maximum after tracheal intubation; (VII) maximum attained during the anaesthetic; (VIII) minimum value during surgery; and (IX) maximum during final laryngoscopy, pharyngeal suctioning and extubation.

All antihypertensive and anticonvulsant drugs given before anaesthesia were recorded.

RESULTS

Complete records of arterial pressure were obtained from 25 of the 26 subjects; the continuous arterial pressure record chart of patient No. 23 was lost. Patient No. 3 failed to meet the study requirement of age, being younger than 25 years old. Therefore, arterial pressure data and other details obtained from 24 of the 26 patients were analysed and are presented.

Four patients suffered one or more seizures and two were considered imminently eclamptic. Table I charts the patients' age, weight, parity and the differences in arterial pressure before and after laryngoscopy and intubation. Included in this table are details of drug therapy administered either by the referring hospitals or upon arrival in the labour ward.

The mean (±SD) age, weight and parity of the study group were 32.5 (±6.0) years, 79.3 (±14.3) kg, and 4.1 (±1.9) pregnancies, respectively.

Mean (±SD) systolic (SAP), mean (MAP) and diastolic (DAP) arterial pressures recorded for the whole patient group ($n = 24$) are shown in table II. The mean (±SD) increase in SAP for all patients following laryngoscopy and tracheal intubation (calculated as the difference between pre-induction (IV) minus maximum post-induction/intubation (VI) pressures before delivery) was 17.9 (±29.4) mm Hg.

Four patients demonstrated an unmodified response to laryngoscopy and intubation with increases in SAP of > 65 mm Hg following intubation (patients Nos 5, 10, 13 and 18) and one, an increase of 40 mm Hg (No. 14). The mean increase in pressure (SAP) in these five was 62.0 (±12.6) mm Hg.

The equivalent increase in SAP for the remaining 19 patients who demonstrated modified responses ($n = 19$) was 6.3 (±19.6) mm Hg, with one patient sustaining a 30-mm Hg decrease in SAP.

Mean pressure changes (SAP, MAP and DAP) (±SD) for the five subjects showing an unmodified hypertensive reflex response, and for the remaining 19 mothers are detailed in tables III and IV, respectively.

The average differences between maximum SAP upon arrival in theatre (I) and post-intubation SAP (VI) for the three groups of patients outlined above were: all ($n = 24$): −29.4 (±50.1) mm Hg; unmodified ($n=5$): +28.0 (±30.3) mm Hg; modified ($n=19$): −44.5 (±43.0) mm Hg.

The mean changes in arterial pressures measured before fentanyl–droperidol (II) and post-intubation (VI) were: all ($n = 24$): −10.7 (±44.9) mm Hg; unmodified ($n=5$): +35.0 (±32.2) mm Hg; modified ($n = 19$): −24.7 (±40.5) mm Hg.

Comparison of pre-induction (IV) arterial pressures with those obtained after laryngoscopy, suction and extubation (IX) in tables II, III and IV indicates that the latter manoeuvres resulted in

TABLE I. *Individual patient data (maternal/neonatal) of 24 hypertensive parturients presenting for emergency Caesarean section under droperidol–fentanyl supplemented general anaesthesia. TSR = Time to sustained respiration * Eclampsia; ** imminent eclampsia; † neonatal death; int. = tracheal intubation*

Patient No.	Age (yr)	Weight (kg)	Previous pregnancies (parity)	Maximum SAP/DAP, and (MAP), before entry to study (mm Hg)	Change in SAP (mm Hg) pre-induction (IV) to post-induction (VI)	Summary of antihypertensive treatment before entry to study and other relevant data	Fetal weight (kg)	Apgar (A–C) 1 min	Apgar (A–C) 5 min	I–D (min)	U–D (s)	TSR (s)
1	45	73	6	190/130 (150)	20	Sodium gardinal 200 mg i.m. Hydrallazine 6.25 mg i.v. ×2 α-Methyldopa 1000 mg by mouth	2.1	5	8	10	60	90
2	34	120	5	220/140 (167)	15	Pethidine 100 mg Promethazine 50 mg	3.6	6	8	21	60	10
4	30	75	4	200/130 (153)	25	Hydrallazine 12.5 mg i.v.+i.v. infusion for 8 h before operation α-Methyldopa 500 mg by mouth 6-hourly Apresoline 30 mg 8-hourly	1.25†	1 (int.)	4	7	120	360
5	28	72	2	220/125 (157)	70	$MgSO_4$ i.v. only No hydrallazine Trimetaphan i.v. before induction	2.7	7	8	12	90	20
6	27	71	3	210/130 (157)	20	Sodium gardinal 200 mg i.m. Hydrallazine 6.25 mg i.v. α-Methyldopa by mouth Trimetaphan i.v. before induction	2.45	6	8	14	120	20
7	27	68	2	220/160 (180)	10	Hydrallazine 6.25 mg i.v. ×2 Trimetaphan i.v. before induction Infant suffered cyanotic episodes Died day 2	3.2†	1 (int.)	2	10	90	600
8	26	64	3	220/140 (167)	−10	Sodium gardinal 200 mg i.m. $MgSO_4$ i.v. α-Methyldopa by mouth Apresoline by mouth Hydrallazine 25 mg by mouth i.v. Trimetaphan i.v. before induction	1.45	4 (int.)	4	3	45	300
9	45	80	10	230/160 (183)	−20	Sodium gardinal 200 mg i.m. $MgSO_4$ i.v. Trimetaphan i.v. before induction	2.5	1 (int.)	4	9	60	300
10	34	85	4	200/125 (150)	70	Phenobarbitone 30 mg 8-hourly Apresoline 50 mg 8-hourly α-Methyldopa 500 mg 6-hourly Trimetaphan i.v. before induction	1.4	7	8	20	510	10

11**	31	60	3	230/145 (173)	10	$MgSO_4$ i.v. Hydrallazine 12.5 mg i.v. Sodium gardinal 200 mg i.m.	2.3	6	8	11	60	15
12	39	120	2	230/130 (163)	25	α-Methyldopa 500 mg 8-hourly Phenobarbitone 30 mg 8-hourly Trimetaphan i.v. before induction	2.5	8	8	21	180	20
13	27	65	2	230/155 (180)	65	Hydrallazine 6.25 mg i.v. ×3 α-Methyldopa 500 mg by mouth Sodium gardinal 200 mg i.m. Trimetaphan i.v. before induction	2.7	3 (int.)	8	8	60	120
14	36	79	5	185/110 (153)	40	Nil stat Caesarean section	3	2 (int.)	7	19	180	300
15	29	70	4	220/130 (160)	−30	Sodium gardinal 200 mg i.m. Trimetaphan i.v. before induction	3.25	8	8	9	30	60
16**	27	80	4	225/135 (165)	35	Sodium gardinal 299 mg i.m. α-Methyldopa by mouth Hydrallzine i.v. Sodium nitroprusside Trimetaphan i.v. before induction	2.7	5	7	9	60	120
17*	40	80	6	165/95 (135)	5	$MgSO_4$ i.v. Hydrallazine i.v.	1.8	4 (int.)	8	7	180	160
18	26	70	6	200/130 (153)	65	Phenobarbitone 200 mg Hydrallazine 6.25 mg i.v.	1.4	7	7	7	60	60
19	36	96	6	210/130 (157)	15	Sodium gardinal 200 mg i.m.	1.85 2.35	7	8	8	60	60
20*	32	70±	1	250/130 (170)	0	Hydrallazine i.v. infusion $MgSO_4$ i.v. Practolol 1 mg i.v.	3.0	Fresh	Stillborn	3	30	—
21	36	80	4	230/140 (170)	25	$MgSO_4$ i.v. Hydrallazine i.v.	1.65	—	—	15	—	—
22	35	100+	5	210/110 (143)	10	Hydrallazine i.v. infusion $MgSO_4$ i.v. Sodium gardinal i.m.	1.65†	5	7	6	60	200
23*	27	75	3	Records lost	Records lost	$MgSO_4$ 5 g i.m. Hydrallazine 6.25 mg i.v. Diazepam 10 mg i.v.	1.5	3 (int.)	5	10	30	180
24	25	75	3	225/130 (162)	−40	Phenobarbitone by mouth α-Methyldopa by mouth Apresoline by mouth Trimetaphan i.v. before induction	1.0†	2 (int.)	5	—	—	—
25	30	90	5	190/110 (137)	5	α-Methyldopa 250 mg by mouth Phenobarbitone 30 mg 8-hourly Trimetaphan i.v. before induction	3.3	3 (int.)	7	13	50	240
26	40	79	6	250/150 (183)	0	α-Methyldopa + phenobarbitone by mouth $MgSO_4$ i.v. Hydrallazine i.v. infusion	1.8	6	8	6	45	60

TABLE II. *Mean (±SD) SAP, MAP and DAP (mm Hg) in24 hypertensive parturients* (n = 24) *given general anaesthesia for Caesarean section (average increase (IV)–(VI) = 17.9±29.4 mm Hg). Event I = maximum measured before entry to operating room; Event II = on the operating table before injection of NLA supplement; Event III = 5 min after NLA supplement; Event IV = just before induction of anaesthesia; Event V = immediately after induction, but before laryngoscopy; Event VI = maximum immediately after tracheal intubation; Event VII = maximum during surgery; Event VIII = minimum during surgery; Event IX = maximum following suction and extubation*

	Event I	Event II	Event III	Event IV	Event V	Event VI	Event VII	Event VIII	Event IX
SAP	215.0	198.3	183.8	169.0	157 7	186.0	178.7	126.1	204.4
	(20.1)	(23.3)	(18.3)	(23.5)	(28.9)	(40.9)	(27.0)	(26.2)	(32.7)
MAP	159.7	149.8	142.0	129.8	124.7	143.4	140.1	96.8	157.4
	(16.0)	(18.2)	(14.2)	(18.3)	(21.3)	(32.4)	(22.4)	(21.4)	(26.2)
DAP	132.1	125.6	121.0	109.8	108.1	124.2	120.9	82.2	132.8
	(15.8)	(18.0)	(14.2)	(18.1)	(19.3)	(28.8)	(21.0)	(19.9)	(26.6)

TABLE III. *Mean (±SD) SAP, MAP and DAP in five hypertensive pregnant* (n = 5) *patients exhibiting 40–70 mm Hg (mean 62.0±12.6 mm Hg) increases in SAP associated with laryngoscopy and tracheal intubation. Events as table II*

	Event I	Event II	Event III	Event IV	Event V	Event VI	Event VII	Event VIII	Event IX
SAP	207.0	200.0	183.0	175.0	175.0	235.0	210.0	149.0	232.5
	(17.9)	(23.5)	(11.0)	(15.4)	(28.3)	(26.5)	(21.5)	(17.8)	(15.0)
MAP	155.0	152.0	141.0	133.6	139.0	175.0	164.0	113.6	179.3
	(16.3)	(17.7)	(4 4)	(9.5)	(15.7)	(30.1)	(12.0)	(14.3)	(10 7)
DAP	129.0	128.0	120.0	113.0	117.5	155.0	141.0	96.0	152.5
	(16.4)	(16.1)	(3.5)	(8.4)	(10.8)	(13.3)	(8.2)	(13.9)	(15.0)

TABLE IV. *Mean (±SD) SAP, MAP and DAP (mm Hg) in 19 hypertensive mothers* (n = 19) *showing increases in arterial pressure ≤ 35 mm Hg (mean 6.3±19.6 mm Hg; lowest recorded −30 mm Hg) associated with laryngotracheal stimulation. Events as table II*

	Event I	Event II	Event III	Event IV	Event V	Event VI	Event VII	Event VIII	Event IX
SAP	217.1	197.9	184.0	167.4	153.2	164.5	170.0	119.7	196.4
	(20.6)	(23.8)	(20.0)	(25.3)	(28.0)	(50.8)	(21.6)	(24.8)	(32.1)
MAP	161.0	149.3	140.1	129.8	121.0	128.4	133.4	92.2	151.1
	(16.2)	(18.8)	(16.6)	(20.1)	(21.3)	(40.8)	(20.1)	(21.0)	(26.2)
DAP	132.9	125.0	121.3	109.0	104.7	110.3	115.3	78.3	127.1
	(16.0)	(18.8)	(16.0)	(20.0)	(19.8)	(36.4)	(20.0)	(19 9)	(26.9)

significant hypertensive reflex responses in all patients. Placed in their different groups, the mean (±SD) SAP at these times were: all ($n = 24$): 169 (±23.5)→204.4 (±32.7) mm Hg; unmodified ($n = 5$): 175.0 (±15.4)→232.5 (±15) mm Hg; modified ($n = 19$): 167.4 (±25.3)→196.4 (±32.1) mm Hg.

The mean (±SD) induction to delivery (I–D) and uterine incision to delivery (U–D) intervals were 10.6 (±5.2) min and 103.3 (±103.3) s, respectively. Ten neonates were severely depressed (Apgar < 4/8) at 1 min after delivery; all 10 required tracheal intubation during resuscitation. Four neonates remained depressed 5 min after birth (table I).

Mean maternal and fetal blood-gas/acid–base data are shown in table V. The majority of these severely hypertensive mothers exhibited a degree of metabolic acidaemia, with a mean base deficit of 6.9 (±2.7) mmol litre^{-1}, despite adequate arterial oxygenation (mean Pa_{O_2} 21.7 kPa). The presence of significant fetal hypercarbia, hypoxia and metabolic acidaemia is indicated by the umbilical cord blood-gas/acid–base results. These values

TABLE V. *Maternal and fetal blood-gas/acid–base status at delivery (mean ± SD).* *$FI_{O_2} = 0.5$

	Maternal artery	Fetal	
		Umbilical vein	Umbilical artery
pH	7.317 (0.055)	7.181 (0.130)	7.101 (0.58)
P_{CO_2} (kPa)	4.71 (0.52)	7.20 (1.65)	8.10 (2.55)
P_{O_2} (kPa)	21.79 (6.83)*	3.74 (1.49)	1.91 (1.06)
Base deficit (mmol litre^{-1})	6.9 (2.7)	8.4 (5.2)	10.5 (4.1)

include the results obtained from the four neonates who died postnatally.

DISCUSSION

In the King Edward VIII hospital obstetric service, hypertension constitutes the most common cause of maternal mortality, ahead of septic abortion, sepsis and haemorrhage. Of the 24403 deliveries in 1983, 17% of the mothers suffered from hypertension ($n = 4148$ patients). Amongst these, 151 cases of eclampsia were recorded. Our own experience is similar to that of Crowhurst and Rosen (1984), in that at least 50% of the patients presenting with pre-eclamptic toxaemia require delivery by Caesarean section. The management of general anaesthesia for patients with hypertension is, therefore, a considerable clinical challenge in this hospital.

The accelerated induction of anaesthesia in all patients is almost invariably associated with a more marked reflex hypertensive response to laryngoscopy and intubation than is induction for routine anaesthesia. Furthermore, laryngoscopy and intubation in any patient with sustained diastolic arterial pressures of > 120 mm Hg results in an exaggerated reflex hypertensive response (Prys-Roberts, 1984). Hypertension in response to the accelerated induction is also exaggerated in pre-eclamptic/eclamptic patients, and represents the period of greatest potential risk to mother and fetus. Sudden increases in systolic arterial pressure in pre-eclamptic parturients is associated with a significantly increased incidence of cerebral haemorrhage and pulmonary oedema (Fox et al., 1977; Hodgkinson, Hinsain and Hayashi, 1980; Wright, 1983). Furthermore, the potentially lethal rupture of an intracranial aneurysm—should one be present, as is always a possibility in any pregnancy—is more likely to occur during the induction phase than at other times (Gianotta et al., 1986). If the severely hypertensive mother is to survive induction of anaesthesia, every effort has to be made not only to control hypertension, but also to prevent sudden increases in systemic and pulmonary arterial pressures consequent on the accelerated induction.

Wright (1983), in a detailed review of the anaesthetic management of pre-eclampsia/eclampsia, emphasized that the upper limit of cerebral autoregulation of blood flow in normotensive patients is an MAP of about 130 mm Hg. Above these pressures protective cerebral vasoconstriction reflexes are overwhelmed and the blood–brain barrier may be breached. In pre-eclampsia this may give rise to cerebral oedema, manifest clinically in the form of impaired consciousness in the absence of excessive sedation or recent convulsion (A. M. Richards, personal communication). Generalized cerebral oedema and discrete multifocal haemorrhagic lesions so generated can be visualized with computerized axial tomography and in postmortem specimens from patients who die of eclampsia (Richards et al., 1986). Laryngoscopy and intubation in severely hypertensive mothers are frequently accompanied by pressure peaks in excess of these values (Hodgkinson, Hinsain and Hayashi, 1980; Connell, Dalgleish and Downing, 1987).

Despite the known consequences of these pathophysiological sequelae to laryngoscopy and intubation, there is no clearly superior method of general anaesthetic induction for these hypertensive obstetric patients (Hodgkinson, Hinsain and Hyashi, 1980; James, 1982; Wheeler and Harris, 1982; Wright 1983; Marx and Bassell, 1984). At best, the management of hypertensive parturients at induction has been described as empirical (Crowhurst and Rosen, 1984).

Fentanyl demonstrably attenuates sudden increases in arterial pressure during intubation of patients undergoing neurosurgical procedures (Dahlgren and Messeter, 1981). The use of low dose fentanyl ameliorates the pressor response to laryngoscopy in non-pregnant patients (Black, Kay and Healy, 1984) and, even in small doses, fentanyl significantly obtunds the pressor response to tracheal intubation during accelerated induction (Cork et al., 1984). These authors demonstrated a significant inhibition of the increase in plasma noradrenaline concentration in those patients who received fentanyl. A close correlation exists between changes in mean arterial pressure occurring at laryngoscopy and circulating noradrenaline concentration (Derbyshire and Smith, 1984), particularly in hypertensive patients (Low et al., 1986).

In pre-eclampsia, patients exhibit a generalized vasoconstriction with an exaggerated response to vasopressors (Gutsche, 1979). Sustained release of catecholamines reduces uterine blood flow and may further compromise a fetus that is already at risk. Any anaesthetic technique that results in a reduction in circulating noradrenaline concentration would seem preferable for this reason alone.

The dose of fentanyl used by Cork and his colleagues (1984) in non-pregnant patients was approximately twice the mean dose used in our study (2.5–3.0 $\mu g\ kg^{-1}$). However, anaesthetic requirements in pregnancy have been show to be reduced compared with those of non-pregnant patients (Palahnuik, Schnider and Eger, 1974).

The administration of an opioid given i.v. immediately before delivery of the neonate during Caesarean section is traditionally anathema to both obstetrician and anaesthetist. Fentanyl, however, when administered in low doses is free from significant consequences to the neonate when given to mothers within 10 min of delivery (Eisele, Wright and Rogge, 1982). Although the condition of the neonate at birth is generally an important consideration in the choice of anaesthetic agents, in pre-eclampsia and eclampsia the condition of the mother is always the anaesthetist's primary concern (Hibbard and Rosen, 1977). Furthermore, under the circumstances described, the use of pre-delivery opioids can be justified on the grounds of deliberately attempting "intrauterine resuscitation" (Myers and Myers, 1979; Myers and Williams, 1982). The advantages of blunting the pressor reflexes in the mother and thus averting hemiplegia, cardiac failure or death, far outweigh the disadvantages of managing a sedated neonate when an experienced neonatal resuscitation team is immediately available. With this point in mind, we suggest that the technique described is limited to those units with neonatal intensive care facilities and resident neonatologists experienced in the management of sedated neonates.

Pre-eclampsia and eclampsia are known to be associated with materno–fetal mismatching of placental perfusion secondary to variable pathological changes in placental basement membrane and vasculature (Wright, 1983). Without the specific pharmacological data available from maternal and fetal fentanyl concentration in humans, all predictions as to fetal blood and brain concentrations in the circumstances of this study are speculative, although one might anticipate materno–fetal transfer. In the ewe (Craft et al., 1983), the maternal concentrations of fentanyl remained 2.5 times greater than those found in the fetus from 5 to 60 min after injection. Cumulation was avoided in sheep by limiting the number of injections of fentanyl to a maximum of two. Further studies to elicit the transplacental pharmacokinetics of fentanyl and alfentanil in pre-eclampsia and eclampsia are currently in progress.

The pre-induction use of droperidol has been associated with the attenuation of the pressor response to intubation (Curran, Crowley and O'Sullivan, 1980). Denlinger and colleagues (1976), Stoelting (1977, 1978) and Donegan and Bedford (1980) have demonstrated advantages in pre-treating patients with i.v. lignocaine in order to obtund the hypertensive response to intubation.

The assessment of neonates consisted of recording the time to sustained respiration and Apgar (minus colour) scores. These techniques, although crude, do differentiate clearly between those neonates who are in need of immediate resuscitation and those who are not—the specific reason for the introduction of these neonatal assessment methods to clinical practice. These tests do not, however, differentiate between asphyxiated and sedated infants, a purpose for which they were not designed. In order to make this distinction, more sensitive tests are required. The data obtained from maternal and umbilical cord blood samples indicate that a good neonatal outcome based on the Apgar scores could be obtained, provided intrauterine asphyxia had not occurred. Severe disturbances of fetal acid–base ($pH < 7.2$) and blood-gas values were considered to be evidence of intrauterine asphyxia. We found that the use of fentanyl 200 μg i.v. before delivery was not associated with undue neonatal depression in the immediate postoperative period.

The patients in this study were drawn from the hypertensive group thought, from our previous experience (Connell, Dalgleish and Downing, 1987) and from information gleaned from the literature, to be in greatest danger (Lopez-Llera, Linares and Horta, 1976; Moodley, Naicker and Mankowitz, 1983). Connell and his colleagues (1987) reaffirmed the identity of a subgroup of pre-eclamptic patients who represent a considerably greater risk category amongst all pre-eclamptic and eclamptic patients. This group is characterized by being multiparous and 25 years of age or more. All the deaths in their study occurred in this older multiparous group, who also demonstrated more extreme hypertensive responses to the induction of anaesthesia (including laryngoscopy and intubation) (mean increase in SAP 90 mm Hg). The results of that study were of significance to this investigation. Indeed, the unmodified pressor response to laryngoscopy and intubation demonstrated by all the patients in the study by Connell and colleagues (1987), which was undertaken in this unit, had profound implications on the design of the present investigation. All patients in this present study were in this high risk category. In the light of the results consequent to the introduction of fentanyl to the induction sequence of severely hypertensive patients, we felt that the inclusion of a control group who would receive an otherwise similar anaesthetic, but without fentanyl and droperidol, was not ethically justified. Furthermore, because of the variable manifestation of individual organ involvement in severe pre-eclampsia and eclampsia, matching of patients for degrees of renal, cardiopulmonary, hepatic, haematological and cerebral involvement is extremely difficult. Although five of our patients did demonstrate severe pressure peaks during induction, 19 did not. We felt that this was a considerable improvement on the results reported by Connell, Dalgleish and Downing (1987) from this unit where, following a similar anaesthetic technique, but without fentanyl and droperidol, there were marked increases in arterial pressure in response to laryngoscopy and intubation. There were no deaths (in the present study) in this high-risk group who received the fentanyl–droperidol anaesthetic sequence.

The uncontrolled hypertension generated by the induction of anaesthesia in patients 5, 10, 13, 14 and 18 re-emphasizes the need for close cooperation between the obstetric and anaesthetic staff (Craig, 1972). Patient No. 5 had received no anti-hypertension therapy, but had been given magnesium sulphate. The specific drug or drugs used to control hypertension before anaesthesia would not appear to be critical. Provided an effective form of therapy has been initiated, the anaesthetic technique described appears to obtund the hypertensive response to laryngoscopy and intubation in the majority of patients. The experience of this unit is that i.v. bolus doses of 6.25–12.5 g hydrallazine effectively control arterial pressure before transfer to theatre. In addition, magnesium sulphate given i.v. first as a bolus of 4 g, followed by an i.v. infusion of 2 g h^{-1} is used. Fine control of arterial pressure just before anaesthesia may be achieved by the use of an infusion of 0.1% trimetaphan given as incremental bolus doses of 2.5 mg, although other agents have been been used (Wright, 1983; Hood et al., 1985).

Twelve of our patients required supplements of trimetaphan over and above existing therapy to control arterial pressure before induction. The amelioration in pressor responses might, on first inspection, appear to be attributable to the use of trimetaphan rather that fentanyl. However, we have previously consistently used trimetaphan in cases of severe hypertension, in a routine attempt to control hypertensive responses following intubation, with poor results (Connell, Dalgleish and Downing, 1987). These, and the similar disappointing observations made by Hodgkinson and co-workers (1980), do not support the concept that control of hypertensive peaks following intubation can be achieved with trimetaphan alone in cases of *severe* hypertension. Mean arterial pressure is reduced by the use of this agent, but it would not appear to prevent pressure peaks consequent to catecholamine secretion. In effect, trimetaphan reduces the baseline pressure from which peak increases must start. Fentanyl, by inhibiting catecholamine secretion, probably prevents the generation of pressure peaks.

The postoperative management of these patients depended on their preoperative status. Patients who were conscious and alert before operation were allowed to awaken, neuromuscular blockade was antagonized and the trachea was extubated following bolus doses of trimetaphan. Our results, however, indicate that control of arterial pressure at the end of anaesthesia during laryngoscopy, pharyngeal suction and extubation was unsatisfactory. We are, therefore, currently investigating the value of giving a further dose of synthetic opioid just before anaesthesia is discontinued.

In patients who were comatose before induction, the tracheal tube was left *in situ* and artificial ventilation continued for transfer to the neurosurgical unit. Evidence of gross cerebral oedema on CAT scan necessitated admission to the neurosurgical intensive care ward for the appropriate management (Richards et al., 1986).

In conclusion, the results of our preliminary studies presented here, suggest that administration of droperidol 5 mg and fentanyl 200 μg before induction effectively obtunds the usual sympathetic hypertensive response to laryngoscopy and intubation in a significant majority of older, multiparous patients suffering from severe hypertension, who have received antihypertensive therapy before anaesthesia. The use of these agents immediately before delivery would not appear to cause significant neonatal depression in the immediate postoperative period in unasphyxiated (metabolically uncompromised) neonates. We believe that the anaesthetic technique described for the anaesthetic management of this subgroup of high risk hypertensive mothers, bears further consideration, especially in the light of our present clinical experience of more than 200 patients treated in this manner since these data were collected. It must be emphasized that the subgroup of patients studied, namely older multiparae, may represent a patient population that is infrequently observed where antenatal screening facilities are well developed. We wish to emphasize, therefore, that the management of these patients is a major undertaking that requires a wide range of invasive monitoring techniques and skills as well as both adult and neonatal intensive care facilities that are best provided in larger obstetric centres.

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MATERNAL AND NEONATAL RESPONSES TO ALFENTANIL ADMINISTERED BEFORE INDUCTION OF GENERAL ANAESTHESIA FOR CAESAREAN SECTION

W. L. DANN, A. HUTCHINSON AND D. P. CARTWRIGHT

SUMMARY

The cardiovascular response to tracheal intubation was compared in two groups of patients undergoing elective Caesarean section. Both groups received a standard technique of general anaesthesia. One of the groups received alfentanil 10 μg kg⁻¹ 1 min before induction of anaesthesia, the other acted as a control group. In the alfentanil group there was a significant modification of the cardiovascular response to intubation as compared with the control group (P < 0.01). No adverse effect on the neonate was seen. However, a significant increase in the incidence of postoperative nausea occurred in mothers in the alfentanil group (P < 0.05).

An increase in arterial pressure and tachycardia commonly follows laryngoscopy and tracheal intubation under general anaesthesia (King et al., 1951; Millar-Forbes and Dally, 1970; Black, Kay and Healy, 1984). This response is probably of little concern in the majority of patients; however, in those with cardiovascular or intracranial disease, complications may occur (Prys-Roberts et al., 1971; Fox et al., 1977). Patients with eclampsia and pre-eclampsia also fall in this category, and may be at risk if the anaesthetic provokes a further increase in arterial pressure.

Narcotics have been shown to be effective in reducing the cardiovascular response to intubation (Dahlgren and Messeter, 1981; Martin et al., 1982), but concern about neonatal respiratory depression has prevented their use during Caesarean section. The cardiovascular response to intubation is decreased by alfentanil 15 $\mu g\ kg^{-1}$ (Black, Kay and Healy, 1984). The pharmacological profile of alfentanil (short duration of action, high protein binding and low lipid solubility) may offer advantages over the older opioids, as it suggests that neonatal depression will be minimal when it is used in an appropriate dose.

PATIENTS AND METHODS

The design of the study was approved by the hospital ethics committee and informed consent was obtained from all patients after a full explanation of the study and its aims. We stressed that there was a small risk of awareness with this anaesthetic technique, but that it was a technique which was, until recently, considered the standard method of anaesthesia for Caesarean section. Patients about to undergo Caesarean section under general anaesthesia between 36 and 42 weeks gestation, taking no medication other than iron and folate supplements, and who suffered from neither hypertension nor any other intercurrent disease were entered to the trial. These patients in every way fitted the description of "clinically acceptable ideal cases" (Crawford, Burton and Davies, 1972). The patients were then allocated to either control or alfentanil groups by use of a random number table.

The anaesthetic technique was similar in both groups. Premedication was ranitidine 150 mg and 0.03-molar sodium citrate 30 ml by mouth; no sedative was given. All patients were placed supine with a wedge under the right buttock and were pre-oxygenated for 5 min. After preoxygena-

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W. L. DANN, M.B., CH.B., F.F.A.R.C.S.; D. P. CARTWRIGHT, M.B., CH.B., F.F.A.R.C.S.; Derby City Hospital, Uttoxeter Road, Derby, DE3 3NE. A. HUTCHINSON, M.B., B.S., F.F.A.R.C.S., University Department of Anaesthesia, Queen's Medical Centre, University Hospital and Medical School, Clifton Boulevard, Nottingham, NG7 2UH. Accepted for publication: March 27, 1987.

Correspondence to W.L.D.

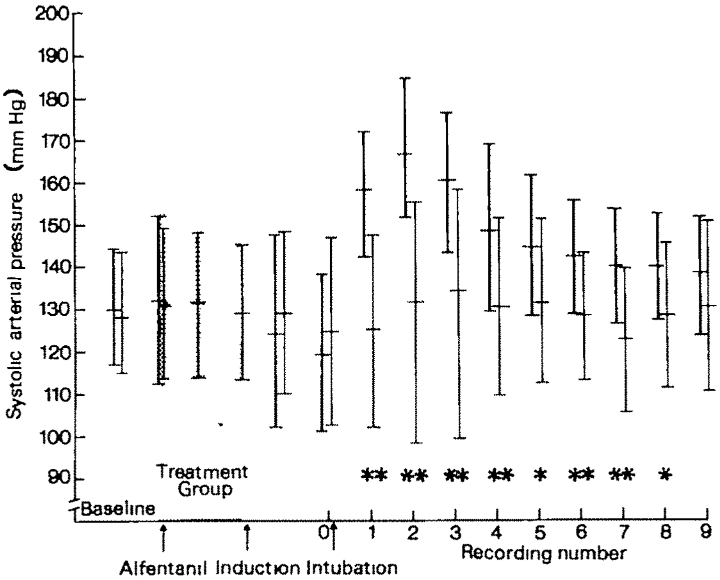

FIG. 1. Changes (±1 SD) in systolic arterial pressure before and after the induction of anaesthesia, in the control group (bold bars) and treatment group (narrow bars). Shaded area represents the time from administration of alfentanil to administration of thiopentone and therefore is of significance only for the treatment group. By *t* test: $^*P < 0.05$; $^{**}P < 0.01$; others not significant.

tion, patients in the treatment group received alfentanil 10 μg kg^{-1} by i.v. bolus injection. One minute later patients in both groups received thiopentone 3.5 mg kg^{-1}. Cricoid pressure was applied as consciousness was lost, and suxamethonium 1 mg kg^{-1} given. Laryngoscopy and intubation were performed 1 min after induction, and the cricoid pressure released after confirmation of the correct placement of the tracheal tube. Anaesthesia was maintained with 50% nitrous oxide in oxygen given by IPPV. End-tidal carbon dioxide was monitored and ventilation adjusted to maintain normocarbia. Neuromuscular blockade was maintained with alcuronium 15 mg. At delivery Syntocinon 10 i.u. was given i.v. and anaesthesia supplemented with papaveretum 15 mg i.v. At the end of the procedure residual neuromuscular block was antagonized by neostigmine 2.5 mg given with atropine 1.2 mg.

Maternal heart rate and arterial pressure were measured throughout using a Dinamap 1846 (Critikon Ltd) and a standard cuff (Cat. no. 8306); a linked printer provided a permanent record. Following a period of 10 min to allow the cardiovascular system to stabilize, recordings were taken at 30-s intervals from the pre-oxygenation period until 5 min following intubation, and at 1-min intervals thereafter.

The neonates were assessed by a paediatrician who was unaware to which group the mother belonged. Apgar scores were awarded at 1 and 10 min. Further routine examinations were carried out 24 h after delivery. On the first day after operation the mothers were questioned about awareness, dreams and postoperative nausea and vomiting.

Data were analysed by the use of paired and unpaired *t* tests, Chi-square tests and analysis of variance. The Mann–Whitney *U* test was used where appropriate. A probability value of $P < 0.05$ was considered significant.

RESULTS

Thirty-seven patients entered the trial; 21 received alfentanil and 16 acted as the control group. The groups were comparable in age, weight, obstetric history and duration of gestation.

Maternal results

There was no significant difference in arterial pressure or heart rate between the groups before the induction of anaesthesia (figs 1, 2 and 3). Neither the administration of alfentanil nor the

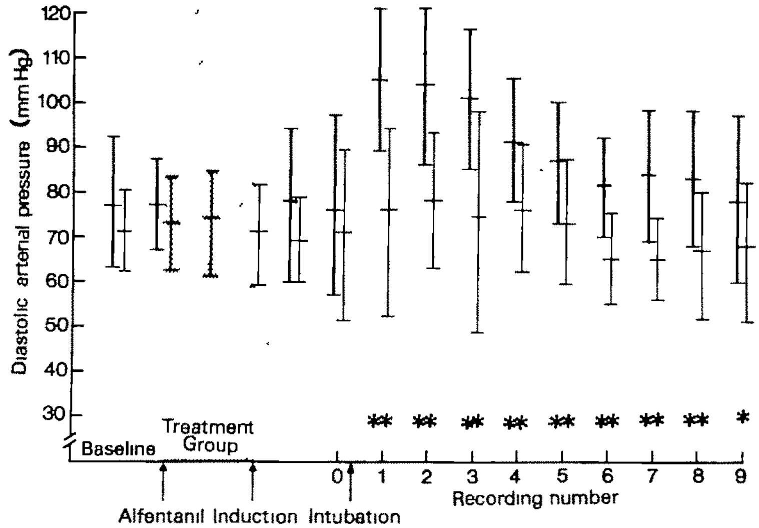

FIG. 2 Changes (±1SD) in diastolic arterial pressure before and after induction of anaesthesia. Explanation as for figure 1.

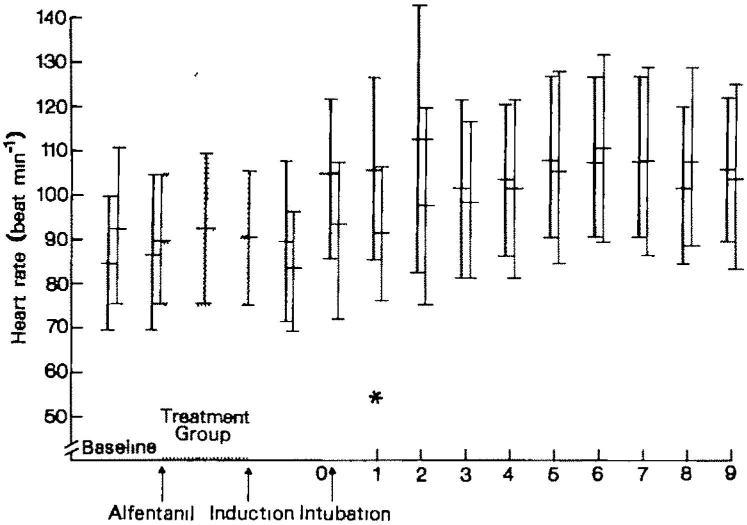

FIG. 3. Changes in heart rate before and after induction of anaesthesia. Explanation as for figure 1.

induction of anaesthesia produced any significant change.

Following intubation there was a significant increase in systolic arterial pressure in the control group (mean systolic AP 166, SD 15 mm Hg, $P < 0.01$) which was not seen in the alfentanil group. The difference between the two groups was significant ($P < 0.01$). In the control group, diastolic arterial pressure increased following intubation (mean diastolic AP 105.5, SD 15 mm Hg, $P < 0.01$). The increase was not seen in the alfentanil group, and again the difference between the groups was significant ($P < 0.01$).

As anaesthesia progressed, both systolic and diastolic arterial pressures in the control group returned towards the baseline values and towards those in the alfentanil group.

No significant change in AP was found after either skin incision or the administration of alcuronium.

There was no significant change in heart rate until after intubation. Following intubation, heart

TABLE I. *Maternal 24-h assessment.* $^*P < 0.05$ *(Chi-square test with Yates' correction for small numbers)*

	Control	Alfentanil
n	16	21
Awareness	2	2
Dreaming	4	6
Vomiting	3	3
Nausea	3	12*

rate in the control group increased by a mean of 40 beat min^{-1} ($P < 0.05$). In the alfentanil group the initial increase in heart rate did not reach statistical significance, but the increase continued and became significant 2 min after intubation. Two patients in each group were aware at some time during the operation (table I), but none of these patients experienced any pain or was particularly distressed by this experience. Dreaming also occurred in 10 patients (four control, six alfentanil). None of the dreams was recalled as unpleasant. The patients had been informed of this possibility at the preoperative visit. The alfentanil group experienced more postoperative nausea (12/21) than the control group (3/16).

Neonatal results

All the neonates were between 36 and 42 weeks gestation. Induction to delivery times were similar in the control (10.4 min ± 2.6) and the alfentanil (11.8 min ± 2.5) groups (table II).

Apgar scores at 1 min (control median 9, alfentanil median 9, $P > 0.1$) and at 10 min after delivery (control median 9, alfentanil median 10, $P > 0.1$) were similar in the two groups.

TABLE II. *Neonatal results*

	Control	Alfentanil
n	16	21
Induction–delivery interval (min) (mean ± SD)	10.4 ± 2.6	11.8 ± 2.5
Weight (g) (mean ± SD)	3280 ± 690	3240 ± 600
Intubated	0	0
Naloxone	0	0
Admitted to Special Baby Unit	1	2
Apgar 1 min		
Median	9	9
Range	4–10	5–10
Apgar 10 min		
Median	10	10
Range	(all 10)	9–10

No neonate in either group required intubation of the trachea or the administration of naloxone.

One neonate in the control group had slight respiratory distress and was observed in the special care baby unit for 24 h. Two of the alfentanil group had prolonged uterine–incision delivery times as a result of obstetric difficulties and were observed in the special care baby unit. No special management was required in any of these subjects.

DISCUSSION

It is difficult to assess the importance of hypertension provoked by tracheal intubation in eclamptic and pre-eclamptic patients. Transient hypertensive episodes of this type often pass unnoticed and morbidity resulting from these episodes is often unreported. The Confidential Inquiry into Maternal Mortality in England and Wales gives little detailed information concerning individual patients. There is little doubt that the hypertension following intubation is important in other disease states in which cerebral oedema is present (Fitch and McDowall, 1969; Shapiro, Galindo and Wyte, 1972). Even though hypertension on intubation is short-lived, complications may follow (Shapiro, Galindo and Wyte, 1972; Fitch and McDowall, 1969; Fox et al., 1979). All our patients were previously normotensive but, even so, two of the control group developed systolic arterial pressures greater than 240 mm Hg following intubation of the trachea (the maximum recorded by the Dinamap). In the previously hypertensive patient the arterial pressure may well increase even more (Prys-Roberts et al., 1971; Fox et al., 1977). To the authors' knowledge, there is no information available on this subject in obstetric patients.

It is known that automated oscillometers can be inaccurate, particularly when recording rapidly (Hutton, Dye and Prys-Roberts, 1984). These inaccuracies are, however, small when compared with the changes in arterial pressure which we observed. Also, at high pressures these devices tend to underestimate and it is, therefore, possible that some of the arterial pressures attained in the control group were even greater than we recorded. We did not consider it ethically acceptable to perform arterial puncture in these healthy parturients in order to obtain recordings of i.a. pressure.

Several methods have been described which reduce the pressor response to intubation (Prys-Roberts et al., 1971; McLeskey et al., 1974; Martin et al., 1982). Some of these are complicated or time consuming and so may be inappropriate in an emergency situation. Complications have been ascribed to some of these techniques (Farnon and Curran, 1981).

Opioids are commonly used in anaesthesia to promote cardiovascular stability. Fears of neonatal respiratory depression have, however, restricted their application at Caesarean section. Alfentanil is rapid in onset and has the shortest duration of action of the currently available opioids, and as such it is most appropriate for the anaesthetic management of brief periods of intense stimulation. Black, Kay and Healy (1984) showed 15 $\mu g\,kg^{-1}$ to be effective in blocking the pressor response to intubation, and our own experience in non-pregnant patients suggested that 10 $\mu g\,kg^{-1}$ was effective. From our results it can be seen that this dose of alfentanil was effective in obtunding the increase in arterial pressure on intubation in the parturient.

In common with the other opioids, alfentanil crosses the placenta, resulting in a maternal: neonatal plasma ratio of approximately 3:1 (H. Waldron, Janssen Pharmaceuticals Ltd, personal communication). Even so, the rapid decline in the maternal plasma concentration with time would be expected to be reflected by a similar decrease in the neonatal plasma concentration. Thus any effects on the neonate would be expected to be brief. This may not be the case with the other opioids. As the average induction to delivery time in our hospital is 11 min, it was reasonable to assume, using the 10-$\mu g\,kg^{-1}$ dose, that the neonatal plasma concentration at delivery would be low. Alfentanil is readily antagonized by naloxone (Helmers et al., 1982). Thus respiratory depression in the neonate, arising from residual narcotic, would be reversed rapidly by naloxone. In the event no evidence of residual narcosis of the neonate was observed in our study, Apgar scores being very similar in the control and alfentanil groups.

We were concerned about the possible additive effects of alfentanil and a volatile agent on the baby, and for this reason volatile agents were not used in this study. Two cases of awareness were observed in each of our groups. Although the numbers are small, this incidence of awareness is comparable to that in other reported series (Crawford, Lewis and Davies, 1985).

In conclusion, our original hypothesis was confirmed. Alfentanil 10 $\mu g\,kg^{-1}$ given before induction of anaesthesia reduced significantly the cardiovascular response to tracheal intubation, without producing any detectable neonatal depression. Hoewever, the incidence of awareness and postoperative nausea suggest that modifications may be necessary to make this technique more acceptable for use in obstetric anaesthesia. Further investigations are, therefore, indicated. The simplicity and effectiveness of alfentanil administration used to control pressor responses may prove beneficial in the anaesthetic management of the parturient.

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HAEMODYNAMIC EFFECTS OF THE I.V. ADMINISTRATION OF CIMETIDINE OR RANITIDINE IN THE CRITICALLY ILL PATIENT

A Double-Blind Prospective Study

C. L. SMITH, D. M. BARDGETT AND J. M. HUNTER

Histamine H_2-receptor antagonists are used commonly to reduce the acidity of gastric contents in critically ill patients who are not receiving enteral nutrition, in an attempt to decrease the incidence of acute upper gastrointestinal haemorrhage (Knight, Bihari and Tinker, 1985).

Cimetidine by mouth is accompanied by a few adverse cardiovascular effects (Boyce, 1981); however, deleterious changes in heart rate and arterial pressure have occurred after cimetidine i.v. in the critically ill patient (Boyce, 1981). Such changes would appear to be transient—lasting for less than 10 min (Iberti et al., 1986). A recent study measuring heart rate and arterial pressure only, suggested that i.v. ranitidine had fewer adverse haemodynamic effects than cimetidine (Breuer et al., 1985).

In a double-blind, cross-over study, we have compared the haemodynamic effects of i.v. cimetidine or ranitidine in critically ill patients. As part of their clinical management, such patients usually require invasive haemodynamic monitoring—including arterial cannulation, central venous catheterization and pulmonary artery catheterization. Only patients in whom such cannulae had already been inserted were considered for inclusion in the study.

SUMMARY

The cardiovascular effects of i.v. cimetidine 200 mg or ranitidine 50 mg were investigated in a double-blind cross-over study of 20 critically ill patients in an intensive therapy unit. Both agents caused transient decreases in mean arterial pressure and systemic vascular resistance, although there was no significant change in heart rate, cardiac output, central venous pressure, pulmonary artery wedge pressure or pulmonary vascular resistance in either group. The hypotensive, systemic vasodilatory effect was more common after cimetidine than after ranitidine. Also, it was significantly greater after cimetidine. Both histamine H_2-receptor antagonists may cause hypotension in the critically ill patient.

PATIENTS AND METHODS

Twenty patients (13 male) were included in the study which had the approval of the hospital Ethics Committee. Clinical details are shown in table I. To be eligible for inclusion, each patient was required to have achieved cardiovascular stability such that the heart rate and arterial pressure had shown little variation during continuous monitoring in the preceding 1 h. Thirteen patients were receiving inotropic agents in the form of dopamine or digoxin alone or in combination, dopamine or dobutamine in combination with isosorbide dinitrate or dopamine combined with dobutamine, to achieve such cardiovascular stability (table I). Another patient (14) who had previously had a bilateral adrenalectomy was receiving an infusion of adrenaline at the time of the study. All patients had been stabilized on the

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C. L. SMITH, M.B., F.F.A.R.C.S.; D. M. BARDGETT,† M.B., F.F.A.R.C S.; JENNIFER M. HUNTER,* M.B., F.F.A.R.C.S.; General Intensive Therapy Unit, Ward 11Z, 11th Floor, Royal Liverpool Hospital, Prescot Street, Liverpool L7 8XP.

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Present addresses:

†Macclesfield District General Hospital, Victoria Road, Macclesfield, Cheshire SK10 3BL.

*University Department of Anaesthesia, Royal Liverpool Hospital, Prescot Street, P.O. Box 147, Liverpool L69 3BX.

Correspondence to J.M.H.

TABLE I. *Details of the patients studied* (n = 20). *All were receiving artificial ventilation except patient 10 who was breathing spontaneously through a tracheal tube with continuous positive airways pressure (CPAP). ARDS = Adult respiratory distress syndrome; MI = myocardial infarction; ARF = acute renal failure*

Patient	Age (yr)	Sex	Clinical details	APACHE II score Admission	Study	Cardiovascular drugs at the time of study
1	65	F	Emergency aortic surgery, ARDS	22	17	Dopamine 6 μg kg^{-1} min^{-1}
2	69	M	*Haemophilus influenzae* pneumonia	23	15	Dopamine 8 μg kg^{-1} min^{-1} + isosorbide dinitrate 3 mg h^{-1}
3	72	M	Pulmonary oedema, post-MI	16	14	Digoxin
4	57	M	Perforated colon, ARF, ARDS, septicaemia	27	18	—
5	68	F	Emergency aortic surgery, ARDS	20	15	Dopamine 2 μg kg^{-1} min^{-1}
6	70	M	Cardiac arrest after MI, pulmonary oedema	29	25	Dopamine 8 μg kg^{-1} min^{-1}
7	71	M	Atypical pneumonia, ARF	36	27	—
8	78	M	Gastrointestinal bleed, ARF, ARDS	22	17	Dopamine 10 μg kg^{-1} min^{-1}
9	65	F	Post-thoracotomy, ARF, ARDS	25	19	Dopamine 5 μg kg^{-1} min^{-1} + isosorbide dinitrate 3 mg h^{-1}
10	39	F	Wegener's granulomatosis ARF following cardiac arrest	23	16	Dopamine 2 μg kg^{-1} min^{-1}
11	55	F	Haemoptysis, cardiac arrest, ARF, ARDS	26	22	Dopamine 12 μg kg^{-1} min^{-1} + dobutamine 8 mg kg^{-1} min^{-1}
12	72	M	Cardiac arrest after MI, pulmonary oedema	29	18	Dopamine 6 μg kg^{-1} min^{-1} + digoxin
13	45	M	Hepatic encephalopathy	25	26	—
14	63	F	Respiratory failure, previous adrenalectomy	27	19	Adrenaline 3 μg min^{-1}
15	69	M	Incisional hernia repair, cardiac arrest from sputum retention	23	32	—
16	39	F	Cardiomyopathy, cardiac arrest after MI	23	16	—
17	76	M	Emergency aortic surgery, aspiration pneumonitis	17	15	Dopamine 2 μg kg^{-1} min^{-1}
18	72	M	Oesophagogastrectomy, fibrosing alveolitis	13	16	Dopamine 4 μg kg^{-1} min^{-1}
19	47	M	Cardiogenic shock after MI	16	8	Dobutamine 15 μg kg^{-1} min^{-1} + isosorbide dinitrate 3 mg h^{-1}
20	56	M	*Aspergillus* pneumonia, ARF, previous renal transplant	27	24	—

inotrope(s) before the study began and were not entered into the study unless the dose of these agents was stable. All patients who satisfied the criteria entered the trial in order of admission to the ITU. A tracheal tube was *in situ* in all patients; 19 patients were receiving intermittent positive pressure ventilation of the lungs (IPPV) and one patient (10) was breathing spontaneously with continuous positive airways pressure (CPAP) at the time of the study.

As an indicator of severity of sickness, APACHE II scores (Knaus et al., 1985) were calculated. The average APACHE II score of the patients studied on admission to the ITU was 24.2 (range 13–36), while the average score at the time of the study was 19.0 (range 8–32).

The study was double-blind. A member of the medical staff not involved in the study diluted cimetidine 200 mg or ranitidine 50 mg to 20 ml with normal saline. The syringes were randomly marked A or B. The code was not broken until the end of the study. As is the usual practice in this ITU, each patient had already received i.v. ranitidine 50 mg 8 hourly after admission to the ITU. The study was, therefore, commenced 8 h after the last dose of ranitidine.

When a patient satisfied the entrance criteria for the study, the following baseline haemodynamic data were recorded: mean arterial pressure (MAP), heart rate (HR), central venous pressure (CVP), mean pulmonary artery pressure (MPAP), pulmonary artery wedge pressure (PAWP) and cardiac output (CO). Systemic vascular resistance (SVR) was derived from the equation:

$$\text{SVR (dyn s cm}^{-5}\text{)} = \frac{\text{MAP (mm Hg)} - \text{CVP (mm Hg)}}{\text{CO (litre min}^{-1}\text{)}} \times 80$$

and pulmonary vascular resistance (PVR) from the equation:

$$\text{PVR (dyn s cm}^{-5}\text{)} = \frac{\text{MPAP (mm Hg)} - \text{PAWP (mm Hg)}}{\text{CO (litre min}^{-1}\text{)}} \times 80$$

Systemic arterial pressure was monitored by percutaneous radial artery catheterization and pulmonary artery pressure by a triple lumen flow directed pulmonary artery catheter (American Edwards Laboratory). The electrocardiograph (ECG), HR, MAP and MPAP were monitored continuously (Simonsen and Weel System, 8000 series) using Medex MX800 pressure transducers. Cardiac output was calculated by the thermodilution technique, using a cardiac output computer (952OA American Edwards Laboratory).

Following the recording of baseline data, the contents of syringe A (20 ml) were administered over a 2-min period by injection to the right atrium via the proximal lumen of the pulmonary artery catheter. HR and MAP only were recorded 1 min after the beginning of the injection and also at 2 min, when the injection was complete. The same recordings were also made at 3, 5, 10 and 15 min after commencement of the injection, together with MPAP, PAWP, CVP and CO. No other drug was administered during the 15 min period of study.

Eight hours later, syringe B was administered, the procedure being the same as for syringe A. However, if the patient's condition had changed significantly, the study was discontinued and, haemodynamic status permitting, was re-initiated the following day with two new preparations of histamine H_2-receptor antagonist. Each patient, therfore, served as his own control. The haemodynamic measurements recorded at each time period were compared with baseline values. The Wilcoxon sign rank test was used for comparison of each result with baseline values and was also used to compare the changes in haemodynamic variables after cimetidine and ranitidine at each time interval. A two-tailed test of significance was used.

RESULTS

The mean values for each haemodynamic variable studied are summarized in tables II and III.

TABLE II. *Mean haemodynamic data (±SD) before and after cimetidine 200 mg i.v. HR = Heart rate (beat min*$^{-1}$*); MAP = mean arterial pressure (mmHg); MPAP = mean pulmonary arterial pressure (mm Hg); PAWP = pulmonary artery wedge pressure (mm Hg); CO = cardiac output (litre min*$^{-1}$*); SVR = systemic vascular resistance (dyn s cm*$^{-5}$*). Statistically significant differences from baseline measurements*: * = $P < 0.05$; ** $P < 0.01$

	Baseline	1 min	2 min	3 min	5 min	10 min	15 min
HR	94.6±17.4	94.8±17.5	95.1±17.8	95.4±17.8	94.5±17.5	94.4±17.6	94.4±17.6
MAP	86.1±10.7	79.3±9.8**	74.6±10 3**	74.7±10.6**	80.6±12.6**	86.0±12.2	87.4±12.2
MPAP	27.4±7.3			26.9±7.6	27.3±7.4	27.9±7.1	28.0±7.3
PAWP	11.2±3.6			10.8±3.6	11.2±3.7	11.2±3.6	11.2±3.7
CO	5.7±1.7			5.7±1.9	5.8±1.8	5.9±1.9	5.9±1.9
SVR	1157±431			986±350**	1066±400**	1133±442*	1164±465
PVR	238±98			238±98	234±97	241±92	242±92

TABLE III. *Mean haemodynamic data (±SD) before and after ranitidine 50 mg i.v. Key as in table II*

	Baseline	1 min	2 min	3 min	5 min	10 min	15 min
HR	97.0±17.3	96.6±16.9	96.4±16.3	94.5±16.8	95.3±16.8	95.3±16.7	95.3±16.8
MAP	86.3±12.8	83.1±12.0*	81 2±11.6**	81 8±12.3	85.3±13.0	87.8±13.5	88.2±13.6
MPAP	27.0±6.9			26.7±7.1	27.5±6.8	27.6±6.9	27 7±6.8
PAWP	10.5±4.3			10.5±4.3	10.9±4.5	10.9±4.4	11.0±4.5
CO	5.6±2.0			5.6±2.0	5.6±2.0	5.8±2.2	5.7±2.1
SVR	1249±544			1188±512	1229±541	1254±573	1258±547
PVR	263±105			263±110	264±114	259±111	258±107

Cimetidine i.v. was associated with significant decreases in MAP at 1 min ($P < 0.01$), 2 min ($P < 0.01$), 3 min ($P < 0.01$) and 5 min ($P < 0.01$) and significant decreases in derived SVR at 3 min ($P < 0.01$), 5 min ($P < 0.01$) and 10 min ($P < 0.05$).

I.v. ranitidine was followed by significant decreases in MAP at 1 min ($P < 0.05$) and 2 min ($P < 0.01$); the decrease in MAP at 3 min did not achieve statistical significance. The mean derived SVR decreased after the injection of ranitidine, but the difference from baseline did not achieve statistical significance.

The effect of cimetidine on MAP was longer lasting than that of ranitidine (fig. 1). Thus MAP had almost returned to baseline values 5 min after commencement of ranitidine administration, but not until 10 min after commencement of cimetidine injection.

There were no significant changes in mean values for HR, MPAP, PAWP, CO, or PVR after either of the drugs. Cardiac rhythm did not vary in any patient.

A marked between-patient variation was found in both the MAP (fig. 1) and SVR changes following cimetidine or ranitidine. The variation appeared to be greater with cimetidine. For example, in 13 patients the decrease in MAP was greater than 10 mm Hg after cimetidine, but in only two patients was this so after ranitidine. In all patients, the hypotensive effect occurred in the presence of minimal changes in cardiac output.

Application of the Wilcoxon sign rank test to a comparison of the change in MAP (ΔMAP) within each individual patient following cimetidine and ranitidine showed a significantly greater decrease with cimetidine at 2, 3 and 5 min ($P < 0.01$). In each of the 11 patients in whom ΔMAP was greater than 5 mm Hg from baseline during or after injection of both agents, the decrease was greater following cimetidine. Similarly, the Wilcoxon sign rank test showed that the decrease in SVR was significantly greater following cimetidine compared with ranitidine at 3 and 5 min ($P < 0.01$). Whilst cimetidine almost invariably was associated with an initial decrease in SVR, ranitidine was less predictable.

In no patient did the decrease in MAP cause circulatory embarrassment such that therapeutic intervention was required. By the end of the study period (15 min), no MAP was greater than 4 mm Hg below baseline value and both groups had 13 patients with MAP above baseline by this time (fig. 1).

DISCUSSION

In critically ill patients, the i.v. administration of cimetidine produced a significant, transient de-

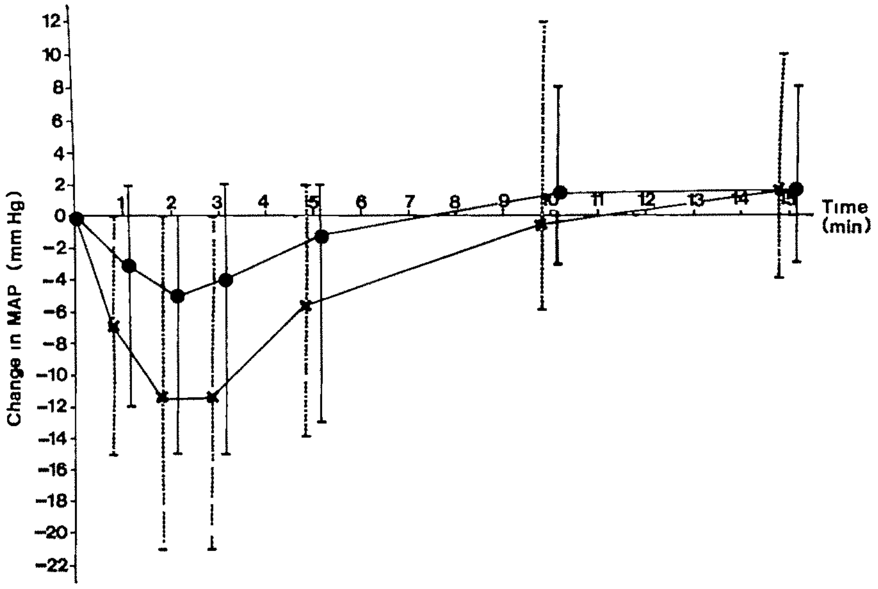

FIG. 1. The mean change in arterial pressure (ΔMAP mm Hg) is given at 1-, 2-, 3-, 5-, 10- and 15-min intervals after the bolus dose of cimetidine (×) and ranitidine (●), together with the range of recordings obtained at each time interval.

crease in MAP of about 10 mm Hg. This was the result of systemic vasodilatation; no change in CO was seen during the 15-min period of study, but SVR decreased markedly (table II). Ranitidine i.v. decreased MAP in some patients, also by a vasodilatory mechanism (table III). The incidence and extent of this decrease in MAP was significantly less after ranitidine than cimetidine (fig. 1). No patient required treatment for the hypotensive effects of these agents.

This study demonstrated considerable variation in the cardiovascular response to both cimetidine and ranitidine between individual critically ill patients. Standard deviations of the mean MAP and SVR at regular intervals after both drugs were large (tables II, III). This variation is almost inevitable when studying critically ill patients and it is a limiting factor in any study performed in this setting. All the patients studied were undoubtedly suffering from severe myocardial depression, usually as a result of septicaemia; several were receiving inotropic agents i.v. (table I). Dopamine is usually the first inotrope we use, especially if renal function is threatened. Dobutamine, up to a dose of 15 µg kg^{-1} min^{-1}, is introduced if an adequate CO is not obtained with dopamine 15 µg kg^{-1} min^{-1}. If both these agents do not produce the required response, adrenaline i.v. is added. It is not uncommon for these inotropes to be continued for several days while recovery of myocardial function subsequent to appropiate antibiotic therapy to control the septicaemia occurs. It was during this period of relative CVS stability that this study was carried out, as we believed it was less likely that the patient's unstable condition could have contributed to the results obtained. In addition, to prevent the influence of any other drugs (eg. antibiotics) on the CVS recordings, these were not given during the period of study.

Breuer and colleagues (1985) have compared the haemodynamic effects of cimetidine and ranitidine in ITU patients in the same dosage and with the same rate of administration as was used in this study, but without the use of a pulmonary artery catheter. A similar effect on MAP was observed, although the degree of change was less than that seen in this study. This may reflect a difference in the degree of morbidity of the patients between the two studies.

Iberti and colleagues (1986) studied only cimetidine in a larger dose (300 mg). When it was administered over a 2-min period, a proportionately greater decrease in MAP in comparison with our findings was observed, again as a result of systemic vasodilatation.

When cimetidine 200 mg was given as an i.v. bolus to patients on cardiopulmonary bypass, the MAP decreased for 3–5 min (Heining et al., 1983). As the myocardial effect on arterial pressure is excluded during cardiopulmonary bypass, the decrease in MAP must have been caused by a decrease in SVR.

In healthy volunteers, neither cimetidine 3.5 mg kg^{-1} nor ranitidine 1.5 mg kg^{-1} given i.v. over 5 min, caused a significant effect on the indices of cardiac function measured non-invasively (Barbat and Warrington, 1980). Even a large dose of cimetidine (800 mg) given i.v. over 1 min did not affect arterial pressure in healthy subjects, although it did increase heart rate (Boyce, 1981). Lee and colleagues (1981) gave cimetidine 400 mg and found a transient but significant decrease in systemic and pulmonary artery pressures in all subjects tested, the changes being more marked in patients with chronic obstructive airways disease than in healthy controls.

It is not difficult to imagine why severe hypotension following i.v. cimetidine has been reported (Mahon and Kolton, 1978; Selby, 1981; Hammond and Ware, 1983). One patient in the study of Iberti and others (1986) had a decrease in MAP from 80 mm Hg to 36 mm Hg following cimetidine 300 mg; volume therapy was required to restore the haemodynamic values. No patient in our study had a decrease in MAP of more than 24 mm Hg after the smaller dose of cimetidine (200 mg), while the greatest decrease in MAP following ranitidine was 15 mm Hg.

In addition to hypotension, there have been reports of other cardiovascular effects of histamine H_2-receptor antagonist therapy. Severe bradycardia has been associated with both cimetidine i.v. (Jefferys and Vale, 1978; Ligumsky, Shochina and Rachmilewitz, 1978) and ranitidine i.v. (Camarri et al., 1982). In addition, i.v. cimetidine has been incriminated in the aetiology of ventricular arrhythmias (MacMahon, Bakshi and Walsh, 1981; Watson, Watson and Keogh, 1982) and asystole (Cohen et al., 1979). Such effects were not observed in this study, but the number of patients was small. Also the inotropic infusions which many of the patients were receiving obscured this effect. The heart and peripheral blood vessels possess H_2-receptors (Anonymous, 1982; Thomas and Misiewicz, 1984) and it is presumed that any change in cardiac rate or rhythm is mediated through these receptors.

Whilst previous studies have shown a decrease in PVR (Lee et al., 1981; Iberti et al., 1986) and mild increases in HR and CO (Boyce, 1981; Iberti et al., 1986), these changes were not observed in this study. Iberti and co-workers (1986) suggested that the usual cardiac compensatory mechanisms that occur following acute vasodilatation (increased HR and CO), are not seen in very ill patients. Certainly, in the healthy volunteers in the study by Boyce (1981) the HR increased significantly with no alteration in arterial pressure following a large bolus dose of cimetidine (800 mg) i.v., suggesting an appropriate cardiovascular response to vasodilatation.

In this study every patient was given a dose of cimetidine 200 mg or ranitidine 50 mg, regardless of weight, age, renal or hepatic function. Thus, blood concentrations could have varied markedly following this fixed dose, which was chosen to be consistent with current clinical practice on this ITU. This factor may also explain in part the wide variation in the changes in MAP and SVR. However, as the cardiovascular effects were so short-lasting, any influence of delayed elimination of these agents on the cardiovascular measurements must have been minimal.

Even when given relatively slowly (over 2 min), i.v. cimetidine 200 mg and ranitidine 50 mg caused significant hypotension in critically ill patients and it would probably be more prudent in the patient with cardiovascular impairment to give such a dose over at least 10 min.

The data sheet for Zantac (ranitidine) injection advises that 50 mg should be given over only 1 min. Although ranitidine caused less hypotension than cimetidine, two patients had decreases in MAP of up to 15 mm Hg with i.v. ranitidine 50 mg over a 2-min period. Consequently, the possibility of hypotension following ranitidine as well as cimetidine in critically ill patients should be remembered, especially if the drug is given over only 1 min. We believe that cimetidine should be diluted and infused i.v. over at least 10 min as cimetidine is more likely than ranitidine to produce an adverse haemodynamic response.

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GASTRIC EMPTYING: A STUDY TO COMPARE THE EFFECTS OF INTRATHECAL MORPHINE AND I.M. PAPAVERETUM ANALGESIA

D. W. ENGLAND, I. J. DAVIS, A. E. TIMMINS, R. DOWNING AND C. W. O. WINDSOR

SUMMARY

Gastric emptying was studied in two groups of 10 patients who underwent elective cholecystectomy. The groups were comparable for age, weight and duration of operation. Gastric emptying was measured with a radioisotopic technique using $Tc^{99}m$-DTPA (diethylene triamine pentaacetic acid) before, and 24 h after, surgery. Analgesia was provided by intrathecal morphine 0.8 mg alone (group A) or by i.m. papaveretum 10 mg, administered as required, plus one additional dose 1 h before the postoperative measurement (group B). Control gastric emptying rates were not significantly different in the two groups (mean ± SD: A = 76.6 ± 23.0 ml; B = 81.8 ± 16.3 ml in 30 min). After surgery, gastric emptying was significantly greater in group A (42.9 ± 35.6 ml) than in group B (11.0 ± 27.9 ml) ($P < 0.05$).

Abdominal surgery frequently produces intolerance of oral fluids in the early postoperative period, necessitating the restriction of fluids by mouth, i.v. fluid replacement and, occasionally, nasogastric aspiration. The cause of this intolerance is incompletely understood and probably multifactorial. However, part of the problem is gastric retention (Dudley, 1968) and it is known that the systemic administration of opioids is one of the major factors in reducing the rate of gastric emptying. Ingram and Sheiner (1981) found that, of several variables, only i.m. opioids (and particularly time elapsed since the last dose) correlated with the decrease in postoperative gastric emptying.

A single injection of intrathecal morphine administered before the induction of a general anaesthetic is effective in providing postoperative analgesia for 24 h in most patients undergoing abdominal surgery (Gjessing and Tomlin, 1981). Our experience suggests that intrathecal morphine may induce less postoperative nausea and vomiting.

We have studied the relative effects of intrathecal morphine and i.m. papaveretum on gastric emptying of fluids after cholecystectomy using a radioisotopic technique.

PATIENTS AND METHODS

Unselected patients scheduled for elective cholecystectomy were randomly allocated to receive either intrathecal morphine (group A) or i.m. papaveretum (group B) for analgesia. Patients giving a history of upper gastrointestinal surgery, peptic ulcer disease, pancreatitis, or who were taking drugs known to affect gastric motility were excluded from the study. Twenty-seven patients were admitted to the trial, but seven were withdrawn: six required exploration of the common bile duct and one had inadequate postoperative analgesia from intrathecal morphine. There were 10 patients in each group. The study was approved by the District Ethical

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D. W. ENGLAND,* M.B., CH.B., F.R.C.S.; I. J. DAVIS, M.B., B.S., F.F.A.R.C.S., D.A.; A. E. TIMMINS, M.SC.; R. DOWNING, M.D., F.R.C.S.; C. W. O. WINDSOR, CH.M., F.R.C.S.; Departments of Surgery, Anaesthetics and Nuclear Medicine, Worcester Royal Infirmary, Ronkswood Branch, Newtown Road, Worcester. Accepted for Publication: March 11, 1987.

Present addresses:
*146, Bath Road, Worcester WR5 3EP.
† Queen Elizabeth Hospital, Birmingham.
Correspondence to D. W. E.

Committee and informed consent was obtained from all patients after each had received a full explanation from one author (D.W.E.) and had been given a second explanation by another (I.J.D.) at the preoperative assessment. On the day before operation, after an overnight fast, the rate of gastric emptying was measured in all patients admitted to the trial. The test was repeated 24 h after surgery, all patients having taken nil by mouth for 3 h.

A standard anaesthetic technique was used. All patients received oral diazepam 10 mg as premedication. Anaesthesia was induced with thiopentone; alcuronium was administered and the patient's lungs ventilated with 30% oxygen in nitrous oxide using a minute volume of 100 ml/kg body weight without added volatile agents. Neuromuscular blockade was antagonized with conventional doses of neostigmine given with atropine. Patients in group A received 0.8 mg of preservative-free morphine in 0.9% saline 4 ml by intrathecal injection at the 2nd lumbar space immediately before induction. After operation they were admitted to a High Dependency Unit for 24 h and excluded from the trial if additional analgesia was required (one patient). In group B, patients received papaveretum i.v. during surgery and by i.m. injection thereafter as required; all were given papaveretum 10 mg 1 h before the second gastric emptying measurement whether they were in pain or not, since Ingram and Sheiner (1981) observed that there was a time relationship between i.m. opioid administration and the rate of gastric emptying. All patients in each group were observed regularly, and treated if in pain.

Cholecystectomy was carried out via a right subcostal incision. Laparatomy, operative cholangiography and subhepatic drainage were performed in all patients.

The technique used for measuring gastric emptying was similar to that described by Ingram and Sheiner (1981). After the required fast, patients were taken to the Nuclear Medicine Department and positioned at 15° to the horizontal under an Elscint Dymax Gamma Camera which was fitted with a general purpose low energy collimator and connected to an Elscint Dycom 80 A/C computer. The patient then drank 100 ml of water (Ingram and Sheiner, 1981) containing 18.5 mBq of $Tc^{99}m$-DTPA (diethylene triamine pentaacetic acid) which is 99.9% unabsorbed when given orally. Water was used as it is the fluid usually introduced first after an abdominal operation. Imaging commenced when isotope appeared in the field of view. Counts were taken every 30 s for 40 min and then summed and stored by the computer. A composite image displaying the maximum counts encountered by every pixel in the study was then displayed on the computer and a region of interest drawn around the stomach by manual control. The computer then generated a time–activity curve for this region and the resulting histogram was displayed. The peak of this histogram, which corresponded to the maximum activity (and, hence, maximum volume of liquid in the stomach) was located and the counts in it noted, along with the counts at the point on the curve corresponding to exactly 30 min later. The maximum count was assumed to correspond to 100 ml, since at this early stage negligible emptying would have occurred. Hence, the volume per count could be calculated and this figure, when applied to the 30-min count, yielded the volume remaining in the stomach at this time, after correcting for radioactive decay. Thus:

$$\text{Volume remaining at 30 min} = \frac{C_{30} \times 100 \times 1.059 \text{ ml}}{C_{\max}}$$

$$\text{Volume emptied in 30 min} = \frac{100 - (C_{30} \times 105.9) \text{ ml}}{C_{\max}}$$

where 1.059 is the correction factor for $Tc^{99}m$ decay at 30 min.

No problems such as vomiting, were encountered, probably because of the relatively small amount of water used.

Sex distribution was analysed by a Chi-squared test and all other results by unpaired *t* test. Statistical significance was assumed when $P < 0.05$.

RESULTS

Groups A and B were comparable for age, weight, sex and duration of surgery (table I). In the period of the study no patient included in group A complained of pain, whereas nine of the 10 group B patients required from one to five (mean 3.5) additional doses of papaveretum. There were none of the reported complications of intrathecal morphine such as delayed respiratory depression, somnolence or itching, and no electrolyte disturbances.

TABLE I. *Details of the two groups of patients (mean values ± SD (range))*

	Group A	Group B
Age (yr)	43 ± 11.0 (22–64)	41 ± 12.3 (22–63)
Weight (kg)	72 ± 15.2 (55–103)	68 ± 12.1 (53–93)
Operation time (min)	48 ± 8.9 (40–65)	45 ± 7.2 (38–55)
Sex	7M/3F	10F

There is a well recognized individual variation in the rate at which normal stomachs empty liquids and this was confirmed (table II). However, the control (mean ± SD) emptying rates (A = 76.6 ± 23.0; B = 81.8 ± 16.3 ml in 30 min) were not significantly different. After surgery, gastric emptying was significantly greater in group A (42.9 ± 35.6 ml) than in group B (11.0 ± 27.9 ml) ($P < 0.05$). In group A the range of values was 0.1–96.0 ml (table II). Four patients showed a decrease of less than 10 ml (the two, 3a and 4a, with greater than control values were assumed to have zero reduction) and one patient (10a) emptied only 0.1 ml in the postoperative period—but had a low control emptying rate. There was almost complete inhibition of gastric emptying (4 ml or less emptied) in eight patients in group B, although one patient (1b) emptied almost as well after (89.7 ml) as before surgery (96.5 ml).

DISCUSSION

The systemic administration of opioids decreases the rate of gastric emptying; the purpose of this study was to ascertain whether the achievement of equivalent analgesia by using opioids intrathecally had the same kind and magnitude of effect. We have demonstrated that almost total inhibition of gastric emptying after cholecystectomy results from the use of systemic opioids (table II). This accords with previous studies in normal subjects (Nimmo et al., 1975), women in labour (Nimmo, Wilson and Prescott, 1975) and after abdominal surgery (Nimmo et al., 1978). Similar patients deriving equivalent analgesia for the same period from intrathecal morphine showed a decrease in the rate of gastric emptying, but the change did not achieve the chosen level of significance ($P < 0.05$).

Fluid is emptied from the stomach in an exponential fashion. When fluid first enters the stomach there is an initial "receptive relaxation" phase after which the tone of the fundus and proximal body, increasing to produce a gastroduodenal pressure gradient, is the chief determinant of emptying. Peristaltic contractions in the stomach are co-ordinated by the pacemaker-like action of the gastric slow wave or basic electrical rhythm (BER), a wave of partial depolarization of smooth muscle cells which proceeds from the mid greater curve towards the pylorus approximately every 20 s. Complete depolarization, and hence contraction, depends on the excitability of the muscle cells at the time of a slow wave. This is dependent on the relative amount of vagal activity which decreases the threshold resulting in action potentials and contraction, and sympathetic activity or adrenaline which increase the threshold and inhibit contraction.

The constipating action of opioids has long been known and utilized in antidiarrhoeal agents. The general effect of opioids on the bowel is to

TABLE II. *Volume (ml) of water emptied from the stomach in 30 min by individual patients before and after cholecystectomy*

Group A (intrathecal morphine)			Group B (i.m. papaveretum)		
Patient	Before	After	Patient	Before	After
1a	97.7	14.1	1b	96.5	89.7
2a	93.5	83.6	2b	96.5	0.0
3a	91.6	96.0	3b	93.9	0.0
4a	90.7	93.7	4b	92.9	0.0
5a	90.7	29.4	5b	90.8	3.3
6a	89.7	12.4	6b	85.5	0.6
7a	68.7	38.6	7b	82.3	0.0
8a	67.0	20.0	8b	69.9	12.4
9a	46.8	40.6	9b	56.8	4.0
10a	29.8	0.1	10b	53.0	0.0

produce an increase in smooth muscle tone, but to decrease effective propulsive contraction. Opioid receptors, endorphins and enkephalins are widespread in the central nervous system. They are also found throughout most of the gastrointestinal tract and in especially high concentrations in the gastric antrum and proximal duodenum (Polak and Bloom, 1979). Enkephalins are found mainly in the myenteric plexus, where they probably act as neurotransmitters within the enteric ganglia. Edin and colleagues (1980) have shown that local intra-arterial infusion of morphine to the pylorus of the cat produces a decrease in gastric emptying similar to that caused by cervical vagal stimulation, and that both these effects are blocked by naloxone. Intracerebroventricular injection of minute quantities of morphine inhibits gastrointestinal propulsive activity (Porreca et al., 1983) and this effect is abolished by intracerebroventricular injection of opioid antagonists (Parolaro, Sala and Gori, 1977) and vagotomy (Stewart, Weisbrodt and Burks, 1978). Clearly, in each of our patients there was the potential for central and peripheral inhibition of gastric emptying.

Morphine administered intrathecally is thought to exert its analgesic effect mainly at cord level (Yaksh and Rudy, 1976) and produces effective analgesia in most patients undergoing cholecystectomy (Downing et al., 1985). Nevertheless, rostral spread of the drug, leading to somnolence, itching and respiratory depression, does occur (Gustafsson, Schildt and Jacobson, 1982). Overspill from the neuroaxis to the systemic circulation has been confirmed and measured (Chauvin et al., 1981), although the technique did not distinguish unmetabolized morphine from its principal inactive metabolite, the glucuronide, and the authors used doses of intrathecal morphine one order of magnitude greater than in the present study (200 μg kg^{-1} and 8–15 μg kg^{-1}, respectively).

Within group A there was considerable variation, with a range of 0.1–96.0 ml emptied from the stomach following surgery. Possible explanations for this are: (a) with increasing age the rate of gastric emptying decreases slowly (Horowitz et al., 1984), but even in old age rates remain well within the normal range for young adults; (b) pain may cause reduced gastric emptying (Volans, 1974; Thompson, Richelson and Malagelada, 1983), although here it appeared that pain was adequately treated; (c) duration and severity of operation were cited by Kewenter and Kock (1963) as causes of postoperative ileus, but in the present study all patients had the same operation through a standard incision with little difference in operation time; (d) another possible variable was stress. The upper gastrointestinal tract has a rich sympathetic innervation from the coeliac plexus. Both centrally and peripherally administered sympathomimetic agents have been shown to decrease markedly both gastrointestinal motility and gastric emptying (Rees et al., 1978; Galligan and Burks, 1983). Clark, Holdsworth and Rees (1980) demonstrated a specific β-adrenoceptor role with β-stimulation inhibiting and β-blockade promoting gastric emptying. Recently, Child and Kaufman (1985) showed that the adrenocortical response to surgery (Clarke, Johnston and Sheridan, 1970) could be significantly reduced with the use of high dose (0.5 mg/10 kg) intrathecal diamorphine and that the hyperglycaemic effect of surgery (Clarke, 1970) was delayed. This decrease in stress response was more marked in the postoperative period, suggesting that slow C fibre pain was blocked whereas, during operation, both C and Aδ fibres (which are less affected by morphine) were being stimulated (Yaksh, 1978). It has also been demonstrated that there are decreased concentrations of cortisol in patients after cholecystectomy treated with intrathecal morphine 0.8 mg as opposed to i.m. papaveretum (Downing et al., 1986).

There remains to be explained the one patient in group B whose stomach emptied almost as well after as before surgery. The only difference between her and the remainder of the group was that she required no postoperative analgesia at all apart from the papaveretum 10 mg given as stipulated 1 h before the second gastric emptying measurement. Other group B patients needed an average of 3.5 additional doses. Her low analgesic requirements could imply naturally high concentrations of endogenous opioids, in which case systemic administration might cause only the small (7 %) decrease in gastric emptying that was observed.

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EFFECT OF EXTRADURAL MORPHINE ON SOMATOSENSORY EVOKED POTENTIALS TO DERMATOMAL STIMULATION

C. LUND, P. SELMAR, O. B. HANSEN, C. M. JENSEN AND H. KEHLET

SUMMARY

The effect of the extradural (L2–3) administration of morphine 6 mg on early (< 0.5 s) somatosensory evoked cortical potentials (SEP) to electrical stimulation of the L1- and S1-dermatomes was examined in eight patients. Extradural morphine did not influence SEP amplitude. SEP latency did not change, except for a minor increase in the latencies of the onset and the P2 components following S1 stimulation.

The extradural administration of opioid drugs has been used in the management of chronic and acute pain for the past decade. Experimentally, the mechanism of action has been demonstrated to be a direct inhibition of spinal reflexes and the depression of the discharge of dorsal horn nociceptors (Kitahata and Collins, 1981; Homma et al., 1983; Pathak et al., 1984; Willer, Bergeret and Gaudy, 1985). Somatosensory evoked potentials (SEP) (defined as changes in the electroencephalogram following somatosensory stimulation, recorded from the central nervous system using a computer averaging technique (Bromm, 1984a) is an accepted method for the objective assessment of the integrity of sensory pathways and has been used in pain research (Chudler and Dong, 1983). Clinical studies have demonstrated a correlation between subjective pain and the amplitude of SEP, and between the intensity of painful somatic stimulation and the amplitude of the cortical SEP following painful tooth pulp stimulation and laser-induced thermal stimulation (Carmon et al., 1980; Bromm and Sharein, 1982).

The present study investigated the effect of the extradural administration of morphine on cortical SEP following dermatomal electrical stimulation.

PATIENTS AND METHODS

Eight patients were studied (four female) with a mean age of 26 yr (range 19–44 yr). All were admitted to the hospital for elective knee surgery and none had symptoms, signs or a history of neuromuscular disease. Informed consent was obtained from all patients and the Helsinki declaration was respected. The design of the study was submitted to and approved by the ethics committee for the Copenhagen Community Hospitals.

Extradural analgesia

An extradural catheter was inserted (L2–3) and a test dose of 0.5% plain bupivacaine 3 ml was injected to ensure that the catheter was not placed in the subarachnoid space. After 30 min morphine 6 mg (in saline 6 ml) was administered via the catheter. The catheter was used to provide surgical anaesthesia and no complications occurred following the extradural technique.

Stimulation

Electrical stimulation of 0.2 ms duration was applied via a bipolar surface electrode (Dantec/Disa 13 L 22, Copenhagen, Denmark) at a rate of 1.5 s^{-1}. The stimulation electrode covered 7 × 30 mm. Two unilateral areas were stimulated at random. The sensory sural nerve, which innervates mainly the area of the S1 dermatome, was stimulated posterior to the lateral malleolus of the

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Claus Lund, M.D., Ole Bo Hansen, M.D. (Department of Anaesthesiology); Claus Munk Jensen, M.D (Department of Orthopedic Surgery); Henrik Kehlet, M.D., Ph.D. (Department of Surgical Gastroenterology); Hvidovre University Hospital, DK-2650 Hvidovre, Denmark. Peter Selmar, M.D., Department of Clinical Neurophysiology, Glostrup Hospital, DK-2600 Glostrup, Denmark. Accepted for Publication. June 8, 1987.

Correspondence to C.L.

TABLE I. *SEP latency (ms) (mean ± SEM). Influence of lumbar extradural morphine 6 mg on the latencies of the onset and the first positive and negative peaks of the somatosensory evoked potentials following stimulation of the L1 and S1 dermatomes.* $P > 0.1$ *comparing pre- and post-morphine values of all SEP components except onset time and P2 following S1 stimulation.* $^*P < 0.05$

	L1			S1		
	Before	1 h	2 h	Before	1 h	2 h
Onset	22.1 ± 1.5	24.5 ± 2.0	24.0 ± 1.3	38.3 ± 2.3	40.5 ± 2.3	40.8 ± 2.4*
P1	32.4 ± 1.0	32.9 ± 1.1	32.6 ± 1.2	47.6 ± 3.0	48.6 ± 3.2	47.5 ± 3.8
N1	44.1 ± 1.5	45.0 ± 1.9	45.0 ± 1.9	60.9 ± 5.2	62.3 ± 5.1	62.3 ± 5.2
P2	56.5 ± 2.6	57.0 ± 2.7	57.3 ± 2.5	75.3 ± 6.3	77.5 ± 6.4	79.4 ± 6.6*
N2	73.0 ± 3.3	73.8 ± 3.6	73.9 ± 3.6	90.6 ± 9.8	91.6 ± 10.3	94.3 ± 10.4
P3	90.3 ± 4.6	90.5 ± 5.4	92.9 ± 5.7	113.6 ± 13.3	116.0 ± 14.2	116.5 ± 16.0

ankle. The cutaneous sensory nerves of the L1 dermatome were stimulated at the anterior superior iliac spine.

The two sensory areas were stimulated at an intensity of four times sensory threshold (TS). TS was defined as the midpoint between the stimulus intensity needed for just detectable perception of stimulation and for just detectable loss of perception of stimulation. Stimulation before injection of extradural morphine resulted in tolerable pain and was repeated 1 and 2 h after morphine administration (see below). There were no complications associated with the stimulation technique.

Recording

Cortical activity was recorded from platinum needle electrodes (Dantec/Disa 25 G 04) at the midline of the scalp, 2 cm posterior and 5 cm anterior (reference) to the vertex located Cz of the International 10–20 system for EEG recording. During each stimulation procedure 1000 responses were averaged. A Dantec/Disa Neuromatic 2000 neuromyograph (Copenhagen, Denmark) was used for stimulation and recording. The amplifier had a bandpass (−3 dB) of 0.5–1000 Hz, the analysis time was 500 ms. The cortical evoked potentials were analysed and the latency of the onset (0) and the first three positive (P1–P3) and negative (N1–N2) peaks were measured, as were the single peak and total peak-to-peak amplitudes.

SEP recordings were performed before the insertion of the extradural catheter and repeated 1 and 2 h after the administration of the morphine. All recordings were performed before surgery.

Statistics

Changes in SEP were assessed by Student's *t* test for paired data.

RESULTS

The latencies of the components of the cortical SEP following stimulation of the L1- and S1-dermatomes are shown in table I. The latencies of the onset time and of P2 increased significantly following stimulation of the S1-dermatome. In contrast, all other SEP latencies remained unchanged following the extradural administration of morphine. Figure 1 shows the mean amplitude following stimulation at the L1- and S1-dermatomes before, and 1 and 2 h after, morphine administration. No change ($P > 0.1$) in the amplitude in either of the two stimulation positions was seen (table II).

A slight, but insignificant, increase in sensory threshold was observed following extradural morphine (table II). Side effects occurred in two patients—nausea in one and slight pruritus in one.

DISCUSSION

The extradural or intrathecal administration of opioids is often used in the treatment of chronic and postoperative pain. The mechanism is thought to be an effect on the dorsal horn of the spinal cord with suppression of activity in the spinal pathways which transmit nociceptive information in a rostral direction (Homma et al., 1983; Pathak et al., 1984; Willer, Bergeret and Gaudy, 1985). Furthermore, a contributary analgesic effect may be achieved by a central action from the systemic absorption of the opioid (Cousins and Mather, 1984). Changes in SEP to noxious stimulation have been used in pain research. Correlations between subjective pain and changes in cortical SEP amplitude and between stimulation intensity and amplitude of SEP have been reported although no final conclusion has been drawn (Chudler and Dong, 1983).

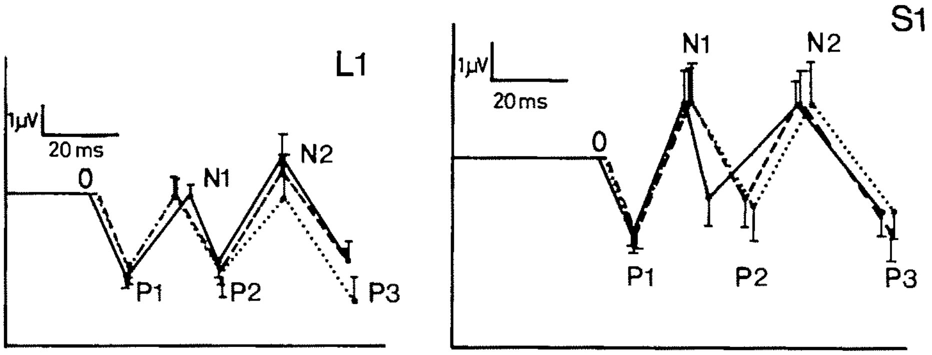

FIG. 1. Mean cortical somatosensory evoked potentials before (——), 1 h (—–), and 2 h (...) after extradural morphine following stimulation at the S1- and L1-dermatomes. $n = 8$ (mean ± SEM).

TABLE II. *SEP amplitude (µV) (mean ± SEM). Influence of lumbar extradural morphine on the amplitudes of components of the early somatosensory evoked cortical potentials and sensory threshold following stimulation of the L1- and S1-dermatomes.* $P > 0.1$ *comparing pre- and post-morphine values of all SEP components*

	LI			S1		
	Before	1 h	2 h	Before	1 h	2 h
P1	1.1±0.1	1.0±0.2	1.0±0.2	2.0±0.3	2.0±0.4	2.0±0.5
N1	1.1±0.1	1.0±0.2	1.0±0.2	3.4±0.8	3.6±0.8	3.5±1.0
P2	0.9±0.2	1.0±0.2	1.1±0.3	2.6±0.7	2.7±0.7	2.8±0.9
N2	1.4±0.3	1.3±0.2	1.1±0.4	2.5±0.6	2.6±0.8	2.8±1.0
P3	1.4±0.2	1.2±0.2	1.4±0.4	2.8±0.6	3.5±0.7	2.9±0.7
Peak to peak	2.2±0.2	2.2±0.3	2.4±0.3	5.2±1.0	5.2±0.8	5.2±1.1
Stim. int.	12.2±1.6	12.2±1.6	12.2±0.6	9.7±1.5	9.7±1.5	9.7±1.5
Sensory threshold	3.0±0.4	3.1±0.4	3.4±0.5	2.4±0.9	2.9±0.5	2.7±0.4

Furthermore, SEP have been used to evaluate the efficiency of various analgesics following i.v. administration (Chapman et al., 1982).

Our study shows that the lumbar extradural administration of morphine changes SEP components with latencies < 120 ms to a very minor degree. The only significant changes demonstrated were an increase in latency to onset and P2 2 h after morphine injection following stimulation of the S1-dermatome. However, the actual delay of the S1-onset was only 2.5 ms (mean). The unchanged latency of P1, which corresponds to the arrival of the nerve signal at the cerebral cortex, argues against the possibility of a spinal delay or block. We found no changes in SEP after stimulation of the L1-dermatome, and the sensory thresholds did not increase significantly during the 2-h study period. We have no explanation for the demonstrated minor effect of extradural morphine on certain S1-latencies. In other studies, the i.v. administration of morphine has been demonstrated to increase the latency and to decrease the amplitude of evoked potentials (Pathak et al., 1984). However, in these studies, morphine was injected i.v., and may merely act as a central depressant compared with extradural administration since the absorption from the extradural space to the blood vessels is slow after extradural administration. Experimental studies have demonstrated that i.v. or intrathecal morphine suppresses noxiously evoked activity of neurones in the dorsal horn (Homma et al., 1983; Kitahata et al., 1974), but in the i.v. study (Kitahata et al., 1974) the doses used were larger and not comparable to those in the clinical studies. In the intrathecal study (Homma et al., 1983) morphine 0.1 mg was applied directly to the spinal cord at an area where single neurones were isolated and recordings were carried out from a microelectrode advanced into the spinal cord. The explanation for the discrepancy between these experimental (Homma et al., 1983) and our clinical results may be dose related, since morphine injected to the extradural space has to pass through the dura to reach the spinal cord and concentrations probably do not reach the values achieved following the direct application of morphine 0.1 mg to spinal neurones. The relative contribution of various nociceptive fibres to the SEP components has been studied and discussed (Bromm 1984b), but no final conclusion has been reached. However, stimuli passing through Aδ-fibres most likely contribute to the early components of SEP while other stimuli passing through C-fibres may evoke potentials with latencies greater than 500 ms (Bromm, 1984b). The thin myelinated (Aδ) afferents terminate in laminae I and V in the dorsal horn of the spinal cord, while C-fibres mainly terminate in lamina II. Autoradiographic studies have demonstrated a high density of staining for opioid receptors in the laminae I and II. Thus, the staining pattern coincides with the termination areas of the C-fibres (Neil and Terenius, 1986).

The relatively large number of opioid receptors in laminae I and II may explain why the cortical SEP in our study remained almost unchanged following extradural morphine, since our method of stimulation probably activates both Aδ- and C-fibres. The afferent impulses may then be transmitted through Aδ-fibres to the CNS. Correspondingly, studies on the endocrine-metabolic stress response to surgery have shown that extradural morphine results in sufficient pain relief, but has no or very little effect on the stress response (Kehlet, 1984). This agrees with our results since extradural morphine had no important effect on SEP amplitude or sensory threshold, indicating no, or very minor, blockade of stimuli transmitted through fast-conducting fibres other than pain fibres. Thus, during surgery, other nociceptive stimuli may presumably pass rostrad through the spinal cord despite the provision of sufficient postoperative pain relief.

In conclusion, the results of our study have demonstrated that the extradural administration of morphine, in doses which normally produce sufficient postoperative pain relief have no, or only a minor, modulatory effect on the early components of SEP following electrical dermatomal stimulation. These findings suggest that extradural morphine has no important inhibitory effect on fast conducting nerve fibre activity, which is in keeping with the minor analgesic effect of morphine during the initial stage of acute surgical stimulation.

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EFFECT OF EXTRADURAL BUPIVACAINE OR I.V. DIAMORPHINE ON CALF BLOOD FLOW IN PATIENTS AFTER SURGERY

G. M. R. BOWLER, M. C. LAMONT AND D. B. SCOTT

SUMMARY

Strain gauge venous occlusion plethysmography was used to measure arterial flow, venous capacity and maximum venous outflow in the calves of seven patients undergoing gynaecological surgery. Plethysmography was performed before surgery, before, and for 30 min after, the extradural injection of 0.5% bupivacaine. On the morning after surgery, 0.5% bupivacaine was injected extradurally and plethysmography performed. With regression of the extradural blockade and the re-emergence of pain, analgesia was produced with diamorphine i.v. and plethysmography repeated. Control measurements were also made. Compared with a mean control value of 100% (3.4 ml dl^{-1} min^{-1}) calf arterial flow increased from 160% to 285% after the preoperative extradural blockade, and from 123% to 191% following the postoperative analgesic extradural blockade, but there was no significant change when pain was relieved after i.v. diamorphine. Mean arterial pressure changed insignificantly after all the injections. No significant changes were measured in venous capacity or maximum venous outflow.

Extradural or subarachnoid blockade with local anaesthetic drugs reduces the incidence of deep venous thrombosis associated with hip replacement surgery (Thorburn, Louden and Vallance, 1980; Modig et al., 1981, 1983b), femoral neck surgery (Davis, Quince and Laurenson, 1980) and open prostatic surgery (Poikolainen and Hendolin, 1983) when compared with an anaesthetic technique using myoneural blockade, controlled ventilation and opioids i.m. given on demand in the postoperative period. In addition, the incidence of pulmonary embolism has been shown to be reduced after total hip replacement (Modig et al., 1981, 1983a). The increase in blood flow to the leg induced by extradural blockade is probably a major factor in this anti-thrombotic action. Since patients undergoing gynaecological surgery for malignancy form another high-risk group for the development of deep vein thrombosis and pulmonary embolism (Bernstein et al., 1980; Clarke-Pearson, Jelovsek and Creasman, 1983; Crandon and Koutts, 1983; Salzman, 1983) the present study was undertaken to provide a within-patient comparison to assess the changes in calf blood flow and vein capacity following extradural blockade in a pain-free state, and on the day after gynaecological surgery, when extradural blockade or diamorphine i.v. was given to provide optimal analgesia.

PATIENTS AND METHODS

Patients

Seven patients undergoing elective total abdominal hysterectomy or uterine myomectomy for benign disease were studied. Approval for the study had been given by the hospital ethics advisory committee. The mean age of the patients was 36.7 yr (range 28–43 yr), the mean weight 64.4 kg (range 43.2–89.1 kg) and the mean height 163 cm (range 156–173 cm).

Premedication consisted of diamorphine 5 mg and atropine 0.6 mg i.m. given 1 h before transfer to the anaesthetic room. An extradural catheter was passed 3–5 cm into the extradural space at the T11/12 space. Ten millilitre of 0.5% bupivacaine was injected over 60 s. Venous occlusion plethysmography was performed before, and for 30 min

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G. M. R. BOWLER, M.B., CH.B., F.F.A.R.C.S.; M. C. LAMONT, B.SC.; D. B. SCOTT, M.D., F.R.C.P.E., F.F.A.R.C.S.; Department of Anaesthetics, Royal Infirmary of Edinburgh, Lauriston Place, Edinburgh EH3 9YW. Accepted for Publication: February 28, 1986.

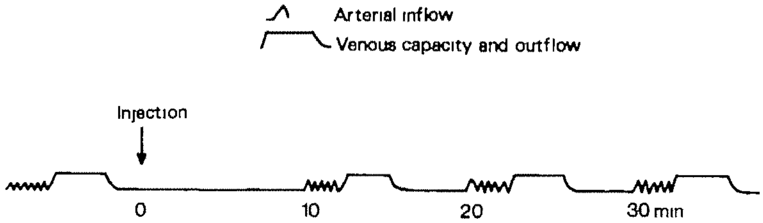

FIG. 1. Plethysmography measurement series.

after, the administration of bupivacaine (fig. 1), then general anaesthesia was induced with thiopentone and maintained with 0.5% halothane and nitrous oxide in oxygen delivered through a face mask. The patients breathed spontaneously. Incremental doses of 0.5% bupivacaine were administered as necessary.

Analgesia after surgery was provided by an infusion of 0.1–0.125% bupivacaine delivered at 15–20 ml h^{-1} until 8.30 a.m. on the day after surgery. Diamorphine 5 mg i.m. as required was also prescribed, the last dose being administered before 6 a.m. The mean requirement was 1.7 injections (range 0–4).

When pain was experienced, usually 2 h after stopping the extradural infusion, an extradural injection of 0.5% bupivacaine 10 ml was given over 60 s. This resulted in good analgesia. Measurements of venous occlusion plethysmography were made. On the return of pain later that day, complete analgesia was achieved using diamorphine i.v. An initial dose of 5 mg was given, followed by 1 mg every 2 min until the patient stated, to direct questioning, that she felt no pain. The mean dose requirement was 8.6 mg (range 6–10 mg). Venous occlusion plethysmography was carried out during this injection.

No fluid load was given with the preoperative extradural blockade. The postoperative i.v. fluid regimen was 500 ml of compound sodium lactate solution alternating with 5% glucose 500 ml, each over 6 h. No patient received blood.

A control series of measurements was also made on the day before surgery or the day before discharge (8 days after surgery) when the patients were ambulant and free of pain and drugs. The timing of the plethysmography measurements was identical to the other series, although no injections were made.

Plethysmography

Using a Medimatic SP2 machine (Medimatic, Hellerup, Denmark) with automatic cuff inflation and deflation and electrical calibration, strain gauge venous occlusion plethysmography of the calves (Whitney, 1953) was performed on four occasions with the patient supine and the legs elevated 15–17.5 cm at the level of the strain gauges. Fifteen-centimetre thigh cuffs were inflated to a pressure of 50 mm Hg. The 38-cm strain gauges were of the single stranded mercury-in-silastic type and were applied with a 2-cm stretch at the level of the calf estimated to have the largest cross-sectional area. On the first application, the position of the strain gauges was marked and the method of application standardized so that their position in the coronal plane and the position of the overlap of the ends was identical in subsequent series, thus avoiding errors attributable to non-uniform limb expansion (Knox et al., 1982). The same two strain gauges were used for all the patients, each strain gauge being used for one side throughout. The legs were exposed to the ambient temperature for 15 min before recordings were started.

Measurements of arterial inflow, the venous capacity after 4 min of cuff inflation, and maximum venous outflow were made (fig. 2) by one of us (M.C.L.) who was blind to the treatments.

The mean arterial pressure (MAP) was measured at 5-min intervals using a Critikon Dinamap 845 machine.

Where percentage values are given, the baseline ("before injection") value of the control series was taken as 100%. For each subject, the percentage value was calculated as follows:

$$100 \times \frac{\text{raw value}}{\text{baseline value}} \%$$

An estimate of calf resistance was calculated for each patient using the following formula:

$$\text{Resistance (kPa litre}^{-1}\text{ s dl}^{-1}\text{)} = \frac{\text{MAP (mm Hg)}}{\text{calf arterial flow (ml dl}^{-1}\text{ min}^{-1}\text{)}} \times 7999$$

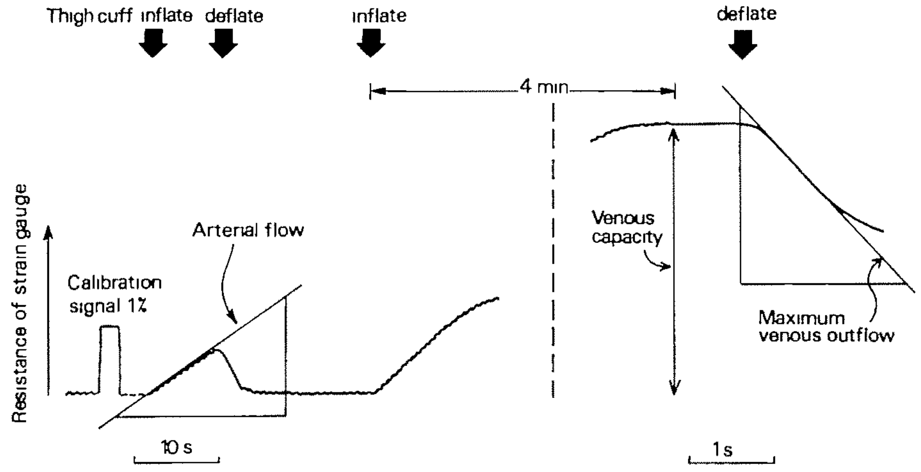

FIG. 2. Illustration of chart recording of one leg and the measurements taken for arterial flow, venous capacity and maximum venous outflow.

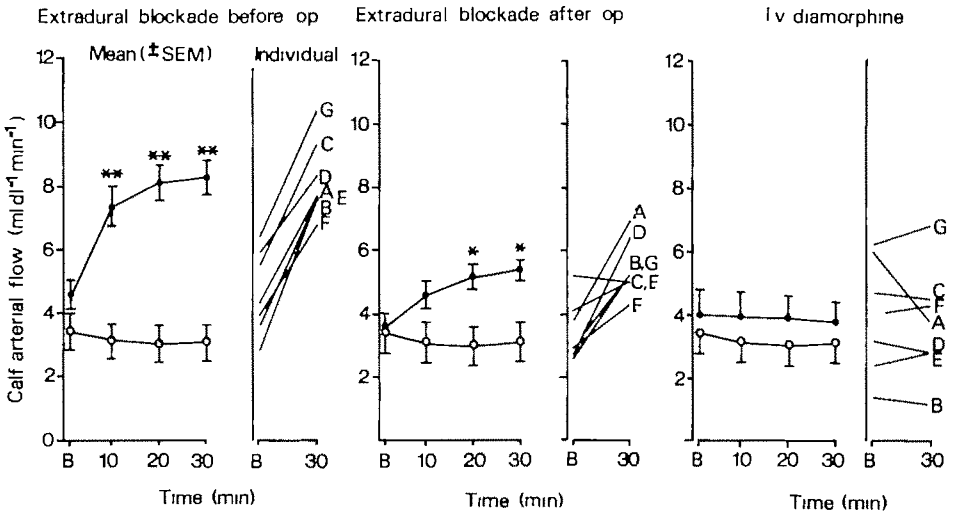

FIG. 3. Calf arterial flow for control (○) and treatment (●) measurement series. $^*P < 0.05$; $^{**}P < 0.01$ for treatment *v.* control using *t* test with Bonferroni correction. B = value before injection.

Statistical analysis

The treatment values were compared with the control values for the corresponding time using Student's paired *t* test with a Bonferroni correction (Miller, 1981). As three *t* tests were performed at each time point, significance at the 5% level was only assumed when the *t* test gave $P < 0.02$, that is 0.05/3.

RESULTS

Calf arterial flow

The values described are the mean of the values for the left and right legs. The value of arterial flow for each leg was the mean of 3–5 slopes. The absolute values obtained are shown in figure 3 and the percentage changes in figure 4.

Before the preoperative injection, leg blood flow

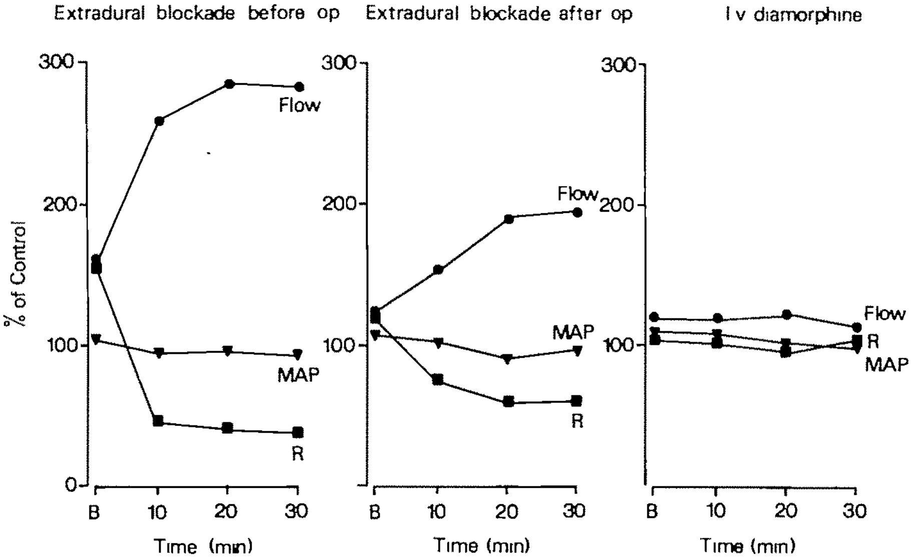

FIG. 4. Calf arterial flow (●), mean arterial pressure (MAP) (▼) and calculated calf arterial resistance (R) (■) where 100 % is the baseline "before injection" control value for each variable. B = Value before injection.

was 4.6 ml dl^{-1} min^{-1} compared with the control value of 3.4 ml dl^{-1} min^{-1}. In spite of this, the extradural injection of bupivacaine further increased leg blood flow to 8.3 ml dl^{-1} min^{-1} 30 min after the injection. The differences between the mean values at 10, 20 and 30 min were significant compared with control values. After surgery, the mean arterial flow was 3.6 ml dl^{-1} min^{-1} before extradural blockade and increased to 5.4 ml dl^{-1} min^{-1} 30 min after the injection of bupivacaine. Compared with the control values, the flow was significantly higher 20 and 30 min after injection.

When the individual percentage changes were averaged, there was a 60 % increase from baseline after premedication and a 183 % increase 30 min after the bupivacaine injection before operation. After surgery, leg blood flow was 123 % of baseline and increased by a further 68 % after bupivacaine injection.

With i.v. diamorphine, the flow was essentially unchanged, being 4.0 ml dl^{-1} min^{-1} before injection and 3.7 ml dl^{-1} min^{-1} 30 min after injection. Compared with the control values, the mean values before and after diamorphine did not differ significantly.

Calf venous capacity

The values obtained are given in table I. The treatment values were less than the control values, but there were no statistically significant differences.

The mean venous capacity at the start of the control period was 3.2 ml dl^{-1} (range 2.2–4.0 ml dl^{-1}). With the preoperative extradural blockade, the venous capacity before injection was 2.8 ml dl^{-1} (86 % of the first control value) and it did not change significantly after injection. After surgery, the values before injection were 2.5 ml dl^{-1} before extradural blockade and 2.4 ml dl^{-1} before diamorphine—decreases of 30 % and 27 %, respectively, from the first control value and, although the changes were not significant,

TABLE I. *Calf venous capacity (ml dl^{-1}) (mean ± SEM) with extradural blockade or i.v. diamorphine. None of the treatment mean values was significantly different from control (Student's paired* t *test)*

	Before injection	After injection 10 min	20 min	30 min
Control (no injection)	3.2 (0.27)	3.4 (0.33)	3.5 (0.38)	3.5 (0.27)
Extradural blockade				
Before operation	2.8 (0.28)	3.2 (0.38)	3.1 (0.22)	3.0 (0.24)
After operation	2.5 (0.38)	2.8 (0.34)	2.9 (0.28)	2.8 (0.31)
Diamorphine i.v.	2.4 (0.53)	2.3 (0.38)	2.8 (0.41)	2.7 (0.43)

TABLE II. *Calf maximum venous outflow* ($ml\ dl^{-1}\ min^{-1}$) (*mean* ± *SEM*) *with extradural blockade or i.v. diamorphine. None of the treatment mean values was significantly different from control* (*Student's paired* t *test*)

	Before injection	After injection		
		10 min	20 min	30 min
Control	69.1	66.7	75.4	79.3
(no injection)	(6.0)	(5.8)	(9.2)	(13.2)
Extradural blockade				
Before operation	69.3	65.8	66.6	70.1
	(7.5)	(4.9)	(6.2)	(6.2)
After operation	59.1	64.9	67.9	61.8
	(6.8)	(6.6)	(7.1)	(7.7)
Diamorphine i.v.	52.3	57.7	59.7	59.4
	(9.5)	(8.6)	(7.9)	(6.8)

TABLE III. *Mean arterial pressure* (*mm Hg*) (*mean* ± *SEM*) *with extradural blockade or i.v. diamorphine. None of the treatment mean values was significantly different from control* (*Student's paired* t *test with Bonferroni correction*)

	Before injection	After injection		
		10 min	20 min	30 min
Control	85.1	87.9	85.6	87.8
(no injection)	(3.0)	(3.5)	(3.1)	(6.1)
Extradural blockade				
Before operation	88.9	79.7	78.8	76.7
	(4.9)	(3.4)	(2.1)	(2.1)
After operation	94.5	85.9	76.6	80.7
	(4.3)	(3.5)	(4.1)	(3.8)
Diamorphine i.v.	93.5	89.9	84.9	85.1
	(2.7)	(2.7)	(4.1)	(3.5)

TABLE IV. *Heart rate* (*beat* min^{-1}) (*mean* ± *SEM*) *with extradural blockade or i.v. diamorphine. Comparisons using Student's paired* t *test with Bonferroni correction are made with the control value*: $^{**}P < 0.01$; $^{*}P < 0.05$

	Before injection	After injection		
		10 min	20 min	30 min
Control	71.9	75.2	73.0	73.2
(no injection)	(4.5)	(5.9)	(4.3)	(4.9)
Extradural blockade				
Before operation	92.9*	93.6	88.2	87.7
	(6.0)	(6.1)	(4.1)	(3.7)
After operation	81.0	84.9	84.3*	81.3*
	(4.6)	(5.3)	(4.6)	(4.4)
Diamorphine i.v.	84.7	82.0	84.0*	84.7**
	(3.9)	(4.3)	(4.3)	(4.2)

there were increases in venous capacity after both extradural blockade and i.v. diamorphine.

Maximum venous outflow

Values obtained are shown in table II. The first control and preoperative maximum venous outflow before injection was 69 ml dl^{-1} (range 50.7–80.7). None of the other values differed significantly, although the values before injection for the postoperative extradural blockade and diamorphine were only 87% and 77%, respectively, of the control values.

Heart rate and mean arterial pressure

The MAP and heart rate recordings are shown in tables III and IV. Compared with control, MAP increased in the postoperative period before injection but, 30 min after both extradural blockade and i.v. diamorphine, MAP had decreased to control values: from 114% to 95% after extradural blockade, and from 109% to 100% after diamorphine. Following the preoperative extradural blockade, MAP decreased from a value of 104% before injection to 93% at 30 min. None of the differences in MAP was significantly different from control.

The heart rate was significantly increased before the preoperative extradural blockade and at 20 and 30 min after the postoperative blockade and i.v. diamorphine. The mean percentage values of MAP, heart rate, calf arterial flow and resistance are shown in figure 4.

Calculated calf arterial resistance

Extradural blockade was associated with significant decreases in resistance 10, 20 and 30 min after injection before and after surgery, but there was no change following i.v. diamorphine. The values are given in table V, and are illustrated as percentages in figure 4.

TABLE V. *Calf arterial resistance* ($(kPa\ litre^{-1}\ s\ dl^{-1}) \times 1000$) (*mean* ± *SEM*) *with extradural blockade or i.v. diamorphine. Comparisons using Student's paired* t *test with Bonferroni correction are made with the control value*: $^{*}P < 0.05$

	Before injection	After injection		
		10 min	20 min	30 min
Control	239.2	260.8	267.2	276.8
(no injection)	(5.2)	(5.1)	(5.2)	(6.1)
Extradural blockade				
Before operation	168.0	92.0*	79.2*	75.2*
	(3.3)	(1.6)	(0.7)	(0.6)
After operation	226.4	155.2*	120.0*	120.0*
	(3.6)	(1.8)	(1.1)	(0.7)
Diamorphine i.v.	229.6	244.8	238.4	240.8
	(8.5)	(8.5)	(8.8)	(8.1)

Room temperature

During each measurement period, the ambient temperature varied by 1 °C or less. The mean temperature during the preoperative measurements in the anaesthetic room was 24.5 °C. The mean ward temperature was 22.5 °C during the extradural "top-up" measurements, 23.5 °C during the i.v. diamorphine measurements and 24.5 °C during the control measurements.

DISCUSSION

Subarachnoid or extradural blockade reduces the incidence of deep venous thrombosis in patients after hip and femoral neck surgery (Davis, Quince and Laurenson, 1980; Modig, Malmborg and Karlstrom, 1980; Thorburn, Louden and Vallance, 1980; Modig et al., 1981, 1983b) and after open prostatectomy (Hendolin, Mattila and Poikolainen, 1981; Poikolainen and Hendolin, 1983) when compared with the incidence after an anaesthetic technique using controlled ventilation followed by parenteral opioids "as required" for postoperative analgesia. A reduced incidence of pulmonary embolism was also demonstrated by Modig and colleagues (1981, 1983b) following total hip replacement under lumbar extradural blockade, and by Poikolainen and Hendolin (1983) after retropubic prostatectomy. The three aetiological factors in the formation of thrombus described by Virchow (1856) may be affected by extradural blockade.

Extradural blockade increases deep venous flow velocity (Poikolainen and Hendolin, 1983). By increasing volume flow rate (Cousins and Wright, 1971; Modig, Malmberg and Karlstrom, 1980) into the legs, flow through the common pathway of the proximal deep veins, namely the popliteal, femoral and external iliac veins, is increased. It is the presence of deep vein thrombosis proximal to the calf that gives rise to a serious risk of pulmonary embolism (Kakkar, Flanc and Howe, 1969). In patients undergoing total hip replacement, extradural blockade with 0.5% bupivacaine with adrenaline reduced blood coagulability by decreasing the capacity for activation of factor VIII and improved fibrinolysis in patients undergoing total hip replacement (Modig et al., 1983a). It is not clear if this was caused by the neural blockade or by the local anaesthetic drug. I.v. lignocaine decreased the incidence of deep vein thrombosis after total hip replacement (Cooke et al., 1977) and the leucocyte invasion of damaged canine venous endothelium (Stewart, 1982).

Some authors have suggested that the incidence of formation of deep vein thrombosis after hip replacement is increased with increased blood loss (Loudon et al., 1978) and blood transfusion (Gray and Mackie, 1983) and that extradural blockade or subarachnoid anaesthesia may reduce the incidence of deep vein thrombosis by reducing blood loss and the requirements for transfusion (Modig et al., 1983b).

Previous studies have investigated leg blood flow in patients undergoing hip surgery and open prostatectomy—high risk groups for deep vein thrombosis and pulmonary embolism, but no studies on leg blood flow appear to have been undertaken in patients undergoing gynaecological surgery. Furthermore, the postoperative measurements of blood flow were made shortly (3 h) after surgery (Modig, Malmberg and Karlstrom, 1980), and no comment was made on the quality of analgesia in the opioid group. Patients prescribed opioid analgesia "as required" commonly receive inadequate dosage (Utting and Smith, 1979). As reflex sympathetic discharge to the lower limbs and adrenal catecholamine secretion may result from painful afferent input to the central nervous system, central interruption of the reflex arc by opioids may have been sub-optimal as a result of inadequate dosage.

In this study, diamorphine was given i.v. until optimal (complete) analgesia was obtained and the effect on leg blood flow was compared with that seen after an analgesic dose of 0.5% bupivacaine, on the day following surgery. The caudad extent of the block to pin-prick was at least L2, the cephalad height being in the range T3–T11. Therefore, the sympathetic outflow to the lower limbs (T10–L1) (Warwick and Williams, 1973) was blocked. As sympathetic blockade can outlast analgesia following extradural blockade (Daos and Virtue, 1963), the order of treatments (postoperative extradural blockade/i.v. diamorphine) was not randomized.

Based on the study of Edholm, Fox and Macpherson (1956), the differences in ambient temperature between the measurement series are too small to account for the large changes in arterial flow.

The increase of arterial flow seen after the institution of extradural blockade before surgery was similar to that in Modig's study (Modig, Malmberg and Karlstrom, 1980), as was the lack of significant change in venous capacity and maximum venous outflow, although this may be explained by the small number studied. The calf arterial flow following the pain-relieving postoperative extradural blockade was less than that achieved by the preoperative blockade, although the changes in MAP were similar. The calculated calf arterial resistance decreased with extradural blockade rather more before surgery. The reasons for this are not clear, as the postoperative injections always produced good analgesia. It is possible that, after operation, there are higher plasma catecholamine concentrations which oppose the vasodilatation of the sympathetic blockade. The increases in both MAP and heart rate indicate a greater degree of sympathetic activity. Thus, reduction in overall sympathetic efferent activity, as reflected by MAP (Pflug, Halter and Tolas, 1982), may have been similar, but the predilection for the lower limb sympathetic efferents was relatively less.

While diamorphine provided excellent analgesia with a small decrease in MAP—possibly reflecting decreased sympathetic activity (Pflug, Halter and Tolas, 1982) and a direct vasodilatory effect (Eckenhoff and Oech, 1960)—there was no increase in the lower limb blood flow nor change in the calculated resistance.

After surgery, all patients were experiencing pain before the extradural injection or the i.v. diamorphine, but there was no significantt difference in the arterial flow nor the resistance compared with control. It is likely that residual sympathetic blockade was present in some of the patients on both occasions. A reduction in flow might otherwise have been observed.

Decreased venomotor tone as a result of sympathetic blockade or opioid might be expected to cause increased venous capacity. Although the changes in venous capacity were statistically not significant, the mean values suggest a decrease with pain, relief of which with extradural blockade or i.v. diamorphine was followed by a return to the values before pain was experienced.

The small and insignificant decrease in calf maximum venous outflow after surgery is difficult to explain. Oedema may cause an apparent reduction in maximum venous outflow (Pini et al., 1984), presumably by decreasing tissue elastance. The patients in this study had been in bed for approximately 36 h by the time of the postoperative measurements and a degree of oedema may be anticipated even if it was not obvious clinically. In the presence of deep vein thrombosis, calf maximum venous outflow decreases by over 50% (Barnes et al., 1977; Pini et al., 1984)—a change greater than that seen in the patients in this study.

An editorial (Salzman, 1983) has highlighted the lack of success and adverse effects of treatments such as mini-heparin, warfarin, dextran and aspirin in preventing deep venous thrombosis in patients in high-risk groups, including those requiring pelvic surgery for malignant disease. In these patients, the incidence of deep venous thrombosis is around 40%, and of fatal pulmonary embolism 1–5% (Bernstein et al., 1980; Clarke-Pearson, Jelorsek and Creasman, 1983; Crandon and Koutts, 1983; Salzman, 1983) where deep venous thrombosis is sought using venography or ^{125}I-fibrinogen scanning. Remarkably, no mention was made in Salzman's editorial of the potential role of anaesthetic technique in prophylaxis against deep venous thrombosis and pulmonary embolism.

While the rate of increase in mortality from deep vein thrombosis and pulmonary embolism appears to be decreasing (Butler, Cotton and Roberts, 1983), it has been estimated that potentially preventable thromboembolism may result in 5000–10000 deaths per year in England and Wales (Morris and Mitchell, 1978). The choice of an appropriate anaesthetic technique may contribute to a decline in this mortality in patients with a high risk of pulmonary embolism. The extradural blockade-induced increase in leg blood flow seen after gynaecological surgery and demonstrated in this study may have a role in deep venous thrombosis prophylaxis. A prospective controlled study is required to assess whether extradural blockade used for operation and postoperative analgesia reduces the incidence of deep venous thrombosis and pulmonary embolism following gynaecological cancer surgery compared with other anaesthetic techniques.

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BUPIVACAINE WITH AND WITHOUT ADRENALINE IN INTERSCALENE BRACHIAL PLEXUS BLOCKADE

Studies in Patients with Rheumatoid Arthritis

K. K. PIHLAJAMÄKI AND R. L. P. LINDBERG

SUMMARY

The action of adrenaline on the pharmacokinetics of bupivacaine has been tested during two successive interscalene brachial plexus blocks in 10 patients with rheumatoid arthritis. The mean venous serum C_{max} of bupivacaine after using it with or without adrenaline 1:200000 were 1.49 ± 0.41 μg ml^{-1} and 2.46 ± 0.85 μg ml^{-1}, respectively. In spite of relatively high total serum concentrations, we could not detect any evidence of toxicity from bupivacaine. Significant tachycardia was seen after bupivacaine with adrenaline, but systolic and diastolic arterial pressures did not change significantly in any session. Marked subjective side effects were noticed only after bupivacaine with adrenaline (shivering twice and palpitations once). The serum protein bound fraction of bupivacaine was higher in rheumatic patients than in our healthy controls: 97.1 ± 2.4% and 91.3 ± 3.6%, respectively. Thus bupivacaine as a local anaesthetic agent seems to be even safer in patients with rheumatoid arthritis than in normal healthy volunteers, because of lower free fraction in the former.

The patient with rheumatoid arthritis is a challenge for the anaesthetist: the rheumatoid involvement of the temporomandibular or cervical spine joints may make intubation difficult and, on occasions, impossible. General anaesthesia may be inappropriate, and for the majority of such patients regional techniques are more suitable. Since the patient often requires a number of operations at short intervals it is important to ensure efficacy of the blockade and, to achieve this, near maximum doses of local anaesthetic agents are used frequently.

The anaesthetist should know the possible peak blood concentration associated with each local anaesthetic combination of agent and technique. However, there are differences in the mean blood concentrations of local anaesthetics after various regional procedures (Tucker et al., 1972). Moreover, in the individual the plasma concentration of a drug is dependent on three factors: absorption of the drug from the injection site, distribution of the drug from the blood to the tissues, and elimination of the drug through metabolism and excretion (Widman, 1975). Because these factors can vary from patient to patient, it is easy to understand that, even in association with one anaesthetic technique, the individual plasma concentrations of local anaesthetics can vary enormously (Yoshikawa, Mima and Egawa, 1968).

The first aim of this study was to exclude the great inter-individual variation when testing the action of adrenaline on the pharmacokinetics and pharmacodynamics of bupivacaine during interscalene brachial plexus block in patients with rheumatoid arthritis, by anaesthetizing the same patient twice, once using plain bupivacaine and once bupivacaine with adrenaline. The second aim was to determine if active rheumatoid disease or the anti-rheumatic medication had any effect on the free fraction of bupivacaine in the serum of the patients.

PATIENTS AND METHODS

Six women and four men, all scheduled for orthopaedic upper limb operations because of

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KALEVI K. PIHLAJAMÄKI,* M.D.; RAIJA L. P. LINDBERG, PH.D.; Department of Pharmacology, Institute of Biomedicine, University of Turku, Turku, Finland. (* Also Paimio Hospital, Paimio, Finland). Accepted for Publication: November 19, 1986.

Address for correspondence: Department of Pharmacology, Kiinanmyllynkatu 10, SF-20520 Turku, Finland.

active rheumatoid arthritis, underwent two interscalene brachial plexus blocks at intervals of 3 weeks to 13 months. All the blocks were performed by the same anaesthetist (K.K.P.) The patients were selected so that there were no contraindications to the use of adrenaline. The mean age of the patients was 55 yr (range 27–68 yr), the mean weight 66 kg (49–102.5 kg), and the mean height 164 cm (148–181 cm). All the patients were receiving at least two non-steroidal anti-rheumatism drugs. Eight were also receiving corticosterone medication, and in one patient this was started during the interval between the two sessions. No other major changes in medication were made between the two sessions.

Premedication was diazepam 10 mg by mouth on the preceding evening, and on the morning of the day of operation. All the patients having chronic corticosterone medication also received hydrocortisone 100 mg i.m. on the preceding evening and prednisolone 25 mg i.m. on the morning of operation.

The operations in which plain bupivacaine was used were: synovectomy of the elbow (three), arthrodesis of the wrist (two) and multiple wrist tenosynovectomies plus multiple finger joint synovectomies (five). The operations for which bupivacaine with adrenaline was used were: synovectomy of the elbow (two), arthrodesis of the wrist (three), multiple tenosynovectomies plus synovectomies (four), and one neurolysis of the ulnar nerve. All the patients had a pneumatic tourniquet above the elbow in both sessions.

An interscalene brachial plexus block was performed (Winnie, 1983). No separate block for the intercostobrachial and medial brachial cutaneous nerves was performed routinely, but after completion of the block the injected solution was thoroughly massaged down the neck. The local anaesthetic agent was 0.5% bupivacaine 40 ml, in one series with adrenaline 1:200000 and in the other without adrenaline. In the first series, four of the patients received the plain bupivacaine and six, bupivacaine with adrenaline; in the second session *vice versa*. In both series, six patients received fentanyl 0.1–0.2 mg i.v. before starting surgery, to make it less difficult for the patients to lie immobile for 1–2 h.

The blood samples for the measurement of bupivacaine serum concentration were drawn at 0, 10, 20, 30, 40, 50, 60, 90, 120 and 180 min from a venous catheter placed in a vein in the contralateral arm. The blood samples were kept at +4 °C until centrifuged, and the sera at −20 °C until analysed. The heart rate, and systolic and diastolic arterial pressures, were registered at 0, 10, 20, 30, 40, 50, 60, 90 and 120 min. The patients were requested to report their subjective feelings and side effects, and all were noted.

Serum bupivacaine concentrations were determined with the HPLC method developed earlier by us (Lindberg and Pihlajamäki, 1984). The detection limit of the bupivacaine was 0.02 μg ml^{-1}, the coefficient of variation of intra-assay variability 2.1% and for interassay variability 5.7%. The protein bound fraction of bupivacaine at every individual peak total serum concentration of both sessions was determined by equilibrium dialysis using Visking membrane 20/32 (Kurz, Trunk and Weitz, 1977). As a control we measured the serum protein bound fraction of bupivacaine in a group of normal healthy volunteers participating in another pharmacokinetic study of bupivacaine ($n = 28$).

Statistical comparisons of the serum concentrations and circulatory variables were carried out by using the *t* test for paired samples.

RESULTS

The venous serum concentration of bupivacaine was always greater after the plain bupivacaine, and the difference was statistically significant from 10 to 120 min (fig. 1). C_{max} (the mean of the individual peak serum concentrations of bupivacaine) was 2.46 ± 0.85 μg ml^{-1} (mean ± SD, range 1.36–4.30 μg ml^{-1}) after plain bupivacaine and 1.49 ± 0.41 μg ml^{-1} (range 0.59–2.05 μg ml^{-1}) after bupivacaine with adrenaline. T_{max} values (the times after administration of bupivacaine when the peak serum concentration was achieved) were 29 ± 18 min (mean ± SD, range 10–60 min) and 33 ± 27 min (range 10–90 min), respectively.

At the times corresponding to individual peak bupivacaine concentration, the mean value for protein bound fraction of bupivacaine was 97.1 ± 2.4% (mean ± SD, $n = 19$). When testing our protein binding method in normal healthy volunteers, we found the protein-bound fraction to be 91.3 ± 3.6% ($n = 28$). The free serum concentration of bupivacaine in our rheumatoid patients after plain bupivacaine was 0.08 ± 0.10 μg ml^{-1} (mean ± SD, $n = 9$). In the patient who had the greatest bupivacaine serum concentration in

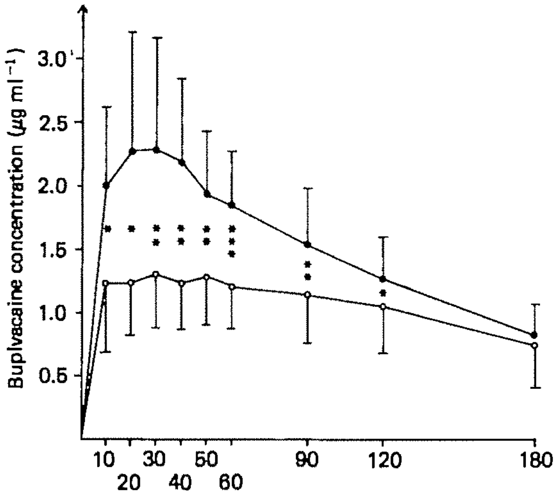

FIG. 1. Serum bupivacaine concentrations (mean ± SD) when using plain bupivacaine 40 ml (●——●) or bupivacaine with adrenaline 1:200000 (○——○) in two successive interscalene brachial plexus blocks of 10 patients with rheumatoid arthritis. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

this study (4.30 μg ml^{-1} at 30 min), the free concentration of bupivacaine was 0.12 μg ml^{-1}.

Circulatory variables are presented in figure 2. Statistically significant changes were few. Only the heart rate was significantly greater than the control value at 10–60 min, when bupivacaine with adrenaline 1:200000 was used. In the same series the diastolic arterial pressure tended to decrease from the control value, but the difference was not significant at any point. One patient had a decrease in arterial pressure from 115/90 to 90/60 at 40 min in the bupivacaine-with-adrenaline series, but this was easily treated with dihydroergotamine 0.5 mg and hydrocortisone 125 mg i.v. At this time the total serum concentration of bupivacaine of the patient was 1.70 μg ml^{-1}.

In spite of relatively high total serum concentrations of bupivacaine, especially after plain bupivacaine, we could not register any side effects related to the toxicity of the bupivacaine (Scott, 1986), even in the patient with maximal serum concentration of 4.30 μg ml^{-1}. Incomplete blockade was experienced on three occasions during the plain bupivacaine series. Two percent lignocaine 5 ml with adrenaline 1:200000 had to be injected once over the axillary artery at 58 min because of the tourniquet, and two patients needed an additional 20 ml of interscalene bupivacaine, at 65 and 45 min, to achieve complete blockade of the ulnar nerve. The bupivacaine serum concentration of the last mentioned patient increased from 1.25 μg ml^{-1} at 40 min to 2.07 μg ml^{-1}at 50 min, only. In both series three patients required additional fentanyl 0.1–0.2 mg i.v. during the operation, mostly because of discomfort induced by the pneumatic tourniquet. In both series, Horner's syndrome was seen five times and recurrent laryngeal block once. When

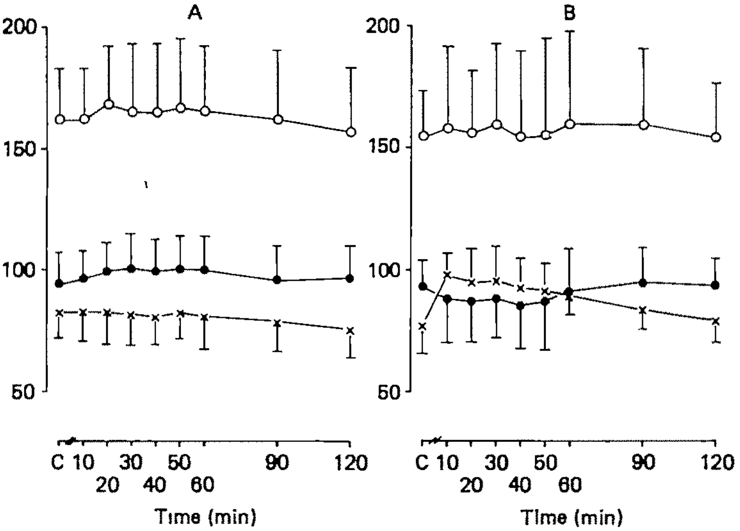

FIG. 2. Systolic (○——○) and diastolic (●——●) arterial pressures and heart rate (×——×) in 10 patients with arthritis when using plain bupivacaine 40 ml (A) or bupivacaine with adrenaline 1:200000 (B) in two successive interscalene brachial plexus blocks (mean ± SD).

bupivacaine with adrenaline was used, two patients had marked shivering, and one patient palpitations. After the first series no patient was unwilling to have the same anaesthetic technique at the subsequent operation.

DISCUSSION

Since there is a close relationship between the systemic blood concentration and the toxic effects of local anaesthetic drugs, measurement of their whole blood or plasma concentrations has become popular. A venous concentration of about 2 μg ml^{-1} has been considered the toxic threshold for bupivacaine in man (Tucker, 1986). In accordance with the present study, however, the plasma concentrations of bupivacaine have in many clinical studies been about 4 μg ml^{-1} without any clear evidence of toxicity (Mather, Long and Thomas, 1971; Ross, Clarke and Armitage, 1980). The reason for the difference may be that most of the toxicity tests are made by giving local anaesthetics slowly i.v. to healthy volunteers and waiting for side effects (Jorfeldt et al., 1968; Mather et al., 1979). The clinical situation is very different.

It has been shown that the rates of absorption of local anaesthetic agents from different anatomical sites vary markedly, because of a multiplicity of factors (Tucker and Mather, 1975; Covino, 1984). After 0.5 % bupivacaine 30 ml (150 mg) with or without adrenaline was given for brachial plexus block, the mean maximal venous plasma concentrations have been 1.2 and 2.2 μg ml^{-1}, respectively (Wildsmith et al., 1977), but it has been shown that the interscalene brachial plexus block is better when using 40 ml of the local anaesthetic agent (Winnie et al., 1979). According to our results, even this higher dose of plain bupivacaine seems to be safe, because the total serum concentrations of bupivacaine in the present study were not very much greater than those reported after bupivacaine 30 ml. In this study all the patients had been selected so that there were no contraindications to the use of adrenaline. Nevertheless, three complained of subjective side effects expressly in those sessions when bupivacaine with adrenaline was used. Thus, there is little reason to use adrenaline in interscalene brachial plexus blocks, since one can use sufficient volumes of 0.5 % plain bupivacaine without risk of toxic serum bupivacaine concentrations. We think the only exceptions are those rare patients who, in the same session, need some other additional local anaesthetic block, for example on the contralateral hand or the feet, and in whom the blood concentration of bupivacaine must be kept as low as possible because of the second anaesthetic procedure.

It is generally accepted that the protein bound fraction of bupivacaine in the plasma is 95 % (Covino, 1984); our results in normal volunteers were $91.3 \pm 3.6\%$ ($n = 29$). According to the present study, this seems to be clearly higher in rheumatic patients ($97.1 \pm 2.4\%$), so the non-protein bound (free) fraction of bupivacaine is clearly smaller in rheumatic patients than in healthy volunteers (2.9 % *v.* 8.7 %, respectively). We think this must mean that the toxicity of bupivacaine at the same total blood concentrations is lower in rheumatic patients than in healthy volunteers. The reason why anti-rheumatic drugs do not affect the protein binding properties of bupivacaine is that bupivacaine, as a basic drug, had binding sites different from those of acidic anti-rheumatic drugs (Benet and Sheiner, 1985). Higher protein binding of bupivacaine in rheumatic patients than in healthy volunteers may be attributable to α_1-acid glycoprotein that can bind bupivacaine (Denson et al., 1984), and is shown to be increased in various inflammatory diseases (Piafsky et al., 1978). Unfortunately, it was not possible for us to measure the α_1-acid glycoprotein values of our patients.

In summary of the present results, interscalene brachial plexus block was a good method for upper limb operations, when using bupivacaine 40 ml as the local anaesthetic agent. The addition of adrenaline to bupivacaine did not offer any advantages. The usefulness of bupivacaine seems to be increased in patients with rheumatoid arthritis when compared with normal healthy volunteers, because the lower-than-normal free fraction of bupivacaine should lead to decreased toxicity without any decreased anaesthetic effectiveness.

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VENOUS PLASMA (TOTAL) BUPIVACAINE CONCENTRATIONS FOLLOWING LOWER ABDOMINAL FIELD BLOCK

J. MARTIN AND R. S. NEILL

SUMMARY

Following local anaesthesia of the lower abdominal wall, in patients undergoing laparoscopic sterilization (n = 16), using 0.5% plain bupivacaine 40 ml (n = 8), or 0.5% bupivacaine with 1:200000 adrenaline (n = 8), venous plasma (total) bupivacaine concentrations were measured (gas–liquid chromatography) at intervals up to 2 h after the local anaesthetic was injected. Mean peak plasma venous concentration achieved following 0.5% plain bupivacaine was 2.23 ± 0.24 µg ml^{-1} (mean ± SEM), while the mean peak concentration following 0.5% bupivacaine with adrenaline was 0.98 ± 0.10 µg ml^{-1} (mean ± SEM). At all sampling times up to and including 45 min after the injection of local anaesthetic, the plasma concentrations were significantly less in the bupivacaine with adrenaline group when compared with the group in whom a plain solution was used.

In general the current view, and the practice, of the concept of balanced anaesthesia consider only the i.v. and the inhalation agents. It is certainly just as reasonable to consider regional anaesthesia as one of the components (Thomson, 1980; Scott, 1983).

The combination of regional anaesthesia (iliac crest and rectus sheath block) with light general anaesthesia offers certain advantages in anaesthesia for laparoscopic investigations in gynaecological surgery. The author's (R.S.N.) personal experience extends to more than 300 patients. The regional nerve block produces anaesthesia of the abdominal wall and underlying peritoneum, light general anaesthesia prevents the response from stimulation of the visceral peritoneum (Lee and Atkinson, 1982; Scott, 1983). The combined technique retains spontaneous ventilation and maintains a firm abdominal wall, giving a more definite end-point to the insertion of the trochar (Seed, Shakespeare and Muldoon, 1970; Collins, Docherty and Plantevin, 1984), and decreases the volume of gas required to create the pneumoperitoneum.

Competitive myoneural blockade in a dose sufficient to permit tracheal intubation may be complicated by delayed antagonism, if the procedure is less than 20 min duration (Pearce, Williams and Jones, 1984) or associated with an unacceptably high percentage of difficulty in intubation if the dose is reduced (Collins, Docherty and Plantevin, 1984; Pearce, Williams and Jones, 1984; Sosis, 1986).

Insufflation of carbon dioxide to the peritoneal cavity leads to an increase in Pa_{CO_2} with either spontaneous or controlled ventilation, with the possibility of exceeding the arrhythmia threshold (Hodson, McClelland and Newton, 1970; Seed, Shakespeare and Muldoon, 1970).

The combination of regional anaesthesia with light general anaesthesia reduces the concentration of volatile agent to the absolute minimum (Scott, 1983), thus decreasing the likelihood of cardiac arrhythmia in the presence of an increased Pa_{CO_2}. If nitrous oxide is used as the insufflating gas a much lower incidence of arrhythmias has been reported (Scott et al., 1972): 4% as compared with 17% with carbon dioxide. Patients in both groups breathed spontaneously.

JOHN MARTIN,* B.SC., M.B., CH.B., F.F.A.R.C.S. (ENG.), Department of Anaesthesia, Ninewells Hospital and Medical School, Dundee. R. S. NEILL, M.D., F.F.A.R.C.S. (I), Division of Anaesthesia, Royal Infirmary, Glasgow. Accepted for publication: June 1, 1987.

*Present address for correspondence: Division of Anaesthesia, Law Hospital, Carluke, Lanarkshire.

Regional anaesthesia is a recommended technique for repair of inguinal hernia in outpatients. Large volumes of local anaesthetic agents have been prescribed and used (Glasgow, 1976; Lee and Atkinson, 1982). Bupivacaine has been recommended in combination with dextran and adrenaline (Simpson, Hughes and Long, 1982); the extended duration of action ensures a more comfortable postoperative period. Plasma concentrations of lignocaine have been measured following its use for anaesthesia of the abdominal wall (Scott and Cousins, 1980); a similar study of the plasma profile of bupivacaine has not been performed.

Scott (1984) highlighted the need for careful investigation of the use of local anaesthetic agents in various clinical situations and for accurate reporting and analysis of any toxic reaction.

This study was undertaken to measure the circulating concentration of bupivacaine following regional nerve block of the lower abdomen, and to determine the effects of using adrenaline on subsequent systemic absorption.

PATIENTS AND METHODS

Sixteen women (ASA I) aged 25–35 yr, undergoing laparoscopic sterilization were informed of the nature of the study, and consent was obtained for venous blood sampling.

All patients were anaesthetized in a standard manner, the only deviation from normal practice being that the trachea was intubated in all patients. This was performed to minimize the possibility of an increase in Pa_{CO_2} resulting from any element of airway obstruction.

Premedication was with temazepan 30 mg unless the patient was a day-case. Following a precurarizing dose of alcuronium 2.5 mg, anaesthesia was induced by the i.v. administration of thiopentone via an indwelling cannula in the dorsum of the hand, and tracheal intubation was facilitated with suxamethonium. Anaesthesia was maintained with nitrous oxide and halothane in 33% oxygen using a Bain anaesthetic system; spontaneous ventilation was permitted for the duration of the procedure (average 20 min).

The patients were allocated to one of two groups and local anaesthesia was performed using either 0.5% plain bupivacaine ($n = 8$) or 0.5% bupivacaine with adrenaline 1 in 200000 ($n = 8$). Bilateral ilioinguinal, iliohypogastric and modified iliac crest blocks were performed: with the patient lying supine, a 20-gauge, 76-mm short bevelled needle was introduced at 45° to the skin surface 1 cm medical to the anterior superior iliac spine, aimed in an infero-medial direction, parallel with the inguinal ligament. The aponeurosis of the external oblique muscle was appreciated, and on advancing the needle, a distinct "click" felt as the needle entered the plane between the external and internal oblique muscles. The needle was then moved more horizontally and advanced between the tissue layers. Ten millilitre of local anaesthetic solution deposited in this plane anaesthetized both the ilioinguinal and iliohypogastric nerves (fig. 1). Before withdrawal of the needle, it was re-directed to lie subcutaneously, cephalad from the point of skin entry and a further 5 ml of anaesthetic agent injected while the needle was withdrawn; this achieved blockade of the cutaneous branches of the lateral divisions of the 11 and 12 spinal nerves. The region of the rectus muscle was blocked by depositing local anaesthetic in the plane between the posterior surface of the recti and the posterior rectus sheaths (fig. 2), bilaterally, two to three finger-breadths below the umbilicus. A total of 40 ml of local anaesthetic was used (200 mg).

Samples of venous blood were obtained from an indwelling cannula in the contralateal arm. Following a baseline sample of 10 ml of venous blood, 10-ml heparinized samples were taken at 5, 10, 15, 20, 30, 45, 60, 90 and 120 min after the block was completed, continuing for 90 min into the postoperative period. The samples were centrifuged and the plasma frozen until analysed for bupivacaine using gas–liquid chromatography. An adaptation of the method of Zylber-Katz, Granit and Levy (1978) was used; this had been described fully elsewhere (Neill and Watson, 1984).

Statistical analysis of the results was performed using Student's *t*-test.

RESULTS

Anaesthesia was uneventful in all patients, and no evidence of a toxic reaction to the local anaesthetic was observed. After recovery from anaesthesia, all the patients had a sensory loss to pinprick over the lower abdominal wall and of the upper thigh. Some patients, however, complained of abdominal cramp, and some of shoulder tip pain; these can be attributed to tubal spasm (tubal clips were used) and peritoneal irritation, respectively.

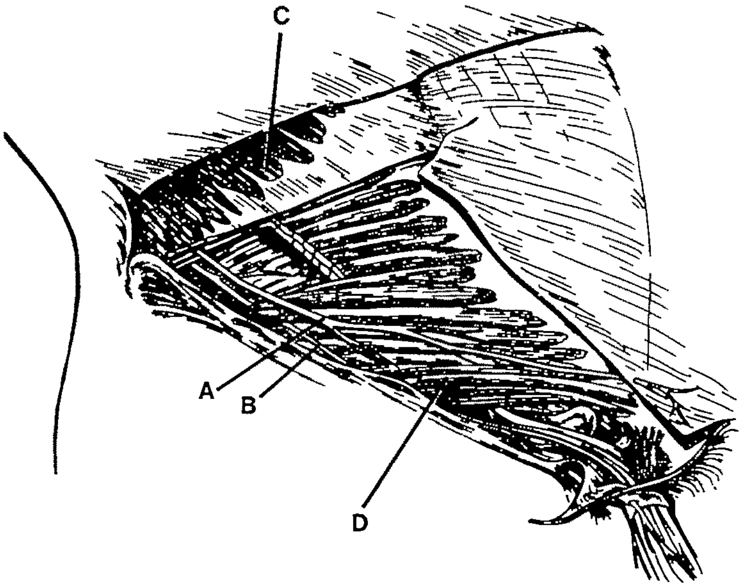

FIG. 1. Anatomy of ilioinguinal and iliohypogastric nerves in the region of the inguinal canal. A = Iliohypogastric nerve; B = ilioinguinal nerve; C = external oblique muscle; D = internal oblique muscle. Adapted from *The Illustrated Handbook of Local Anaesthesia* by Ejnar Eriksson, with kind permission of Lloyd-Luke (Medical Books) Ltd, Publishers.

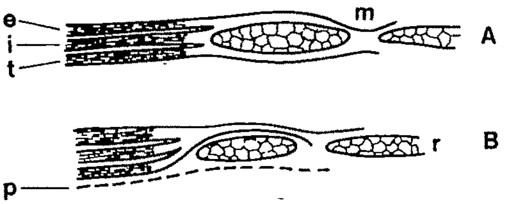

FIG. 2. Rectus sheath in coronal section, A above and B below arcuate line. e = External oblique muscle; i = internal oblique muscle; t = transversus abdominus muscle; p = peritoneum; r = rectus abdominus muscle.

Demographic details are shown in table I.

The results of plasma analysis are demonstrated in table II. The mean peak plasma bupivacaine concentration using the plain solution was 2.23 μg ml^{-1} ± 0.24 (mean ± SEM); that for the solution with adrenaline was 0.98 mg ml^{-1} ± 0.10 (mean ± SEM). The difference is statistically significant ($P < 0.001$).

Plasma concentrations following the injection of plain bupivacaine were significantly greater at all sampling times from 5 to 45 min inclusive.

Peak concentration also was reached in a shorter time with a plain solution (fig. 3).

DISCUSSION

The study demonstrates that, for anaesthesia of the lower abdominal wall, 0.5% bupivacaine 40 ml (3 mg kg^{-1} in this series) neither resulted in clinical evidence of toxicity, nor achieved serum concentrations equal to those considered to cause

TABLE I. *Demographic data (mean values ± SEM). Differences between groups not statistically significant*

Group	Weight (kg)	Age (yr)	Dose of bupivacaine (mg kg^{-1})
Plain bupivacaine ($n = 8$)	64±6.2	28±3	3.38±0.127
Bupivacaine with adrenaline ($n = 8$)	60±2.2	30±4	3.29±0.22

TABLE II. *Mean (± SEM) venous plasma bupivacaine concentrations at various times after injection. t test results, with probabilities* (P)

Time after injection (min)	Bupivacaine concn ($\mu g\ ml^{-1}$) Plain	With adrenaline	t	Probability
0	0	0		
5	0.97 (0.29)	0.24 (0.14)	2.3	$0.05 > P > 0.02$
10	1.22 (0.27)	0.30 (0.10)	3.25	$0.02 > P > 0.01$
15	1.51 (0.27)	0.46(0.11)	3.60	$0.01 > P > 0.001$
20	1.68 (0.24)	0.59 (0.10)	4.29	$0.01 > P > 0.001$
30	1.64 (0.21)	0.67 (0.09)	4.26	$0.01 > P > 0.001$
45	1.72 (0.31)	0.86 (0.10)	2.62	$0.05 > P > 0.02$
60	1.67 (0.35)	0.91 (0.10)	2.09	$0.1 > P > 0.05$
90	1.32 (0.24)	0.79 (0.09)	2.08	$0.1 > P > 0.05$
120	1.03 (0.20)	0.70 (0.08)	1.51	$0.5 > P > 0.1$

serious toxicity (Moore, Balfour and Fitzgibbons, 1979; Sheen and Michenfelder, 1979).

The potential toxicity of local anaesthetic drugs lies not only in the inherent toxicity of the drugs themselves, but also in the many aspects of their clinical use which determine the circulating concentration of the local anaesthetic, for example, the site of injection (Scott, et al., 1972; Neill and Watson, 1984; Thorburn and Moir, 1984), rate of injection (Scott, 1975), concentration of drug used, and the use of vasoconstrictors to reduce systemic absorption (Scott et al., 1972; Scott and Cousins, 1980).

It has been argued that one of the most important factors contributing to the toxicity of local anaesthetic agents is the vascularity of the area to which they are injected (Sheen and Michenfelder, 1979; Neill and Watson, 1984). The tissue planes to which bupivacaine was injected in this study are not highly vascular; furthermore, direct intravascular injection—another reason for toxicity—is unlikely, as the inferior epigastric vessels are the only vessels of significant size in the area to which the injections are made.

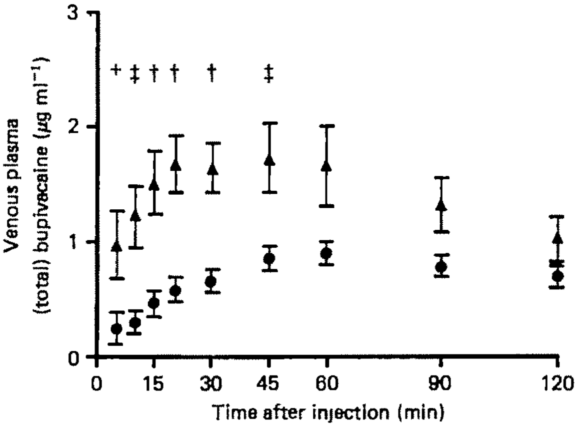

FIG. 3. Mean plasma total bupivacaine concentration (± SEM) for up to 2 h after injection. ▲ = 0.5% Plain bupivacaine; ● = 0.5% bupivacaine with adrenaline 1:200000. + $0.05 > P > 0.02$; ‡ $0.02 > P > 0.01$; † $0.01 > P > 0.001$.

No patient in the study exhibited any sign of cardiovascular or neurological toxicity. Measurements and observations were made during the surgical procedure and continued into the postoperative recovery period. All patients were awake and co-operated fully during the testing of cutaneous anaesthesia which concluded the study.

It is possible that general anaesthesia could have masked signs of minor toxicity during the surgical procedure and the early recovery phase, but the effect must have been minimal or absent in the later period of the study at a time when the plasma concentrations were still at a plateau concentration (fig. 3).

Jorfeldt and colleagues (1968) infused bupivacaine i.v. to mean arterial plasma concentrations of 2 $\mu g\ ml^{-1}$ with no neurological or cardiovascular side effects, the subjects spontaneously remarking that they experienced fewer symptoms than following lignocaine or mepivacaine. Following extrapolation from the plasma concentrations which produced convulsions in dogs they suggested that, in man, the "danger level" was 4 $\mu g\ ml^{-1}$—a figure supported by blood concentrations in patients during convulsions (Moore, Balfour and Fitzgibbons, 1979).

Reynolds (1971) infused bupivacaine i.v. and

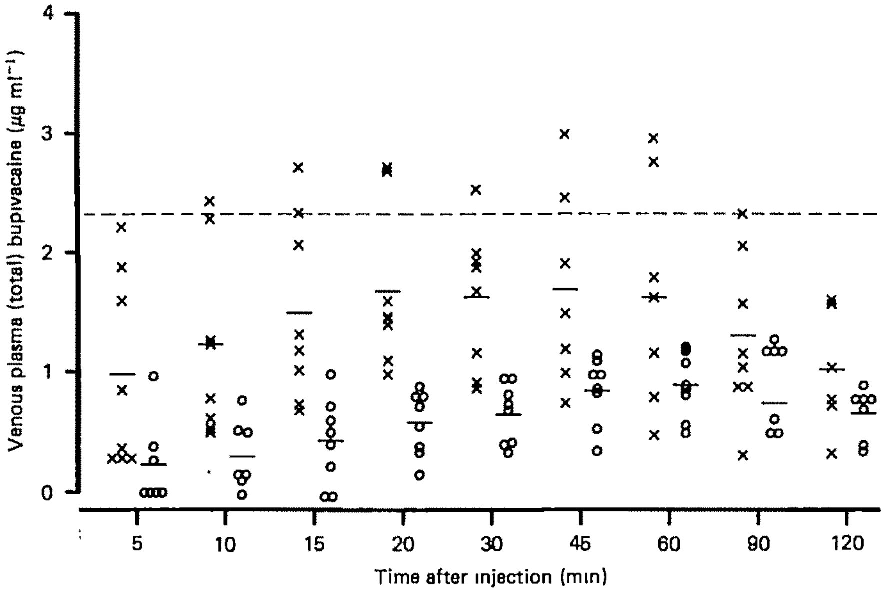

FIG. 4. Venous bupivacaine (total) concentrations up to 2 h after injections. × = Plain bupivacaine 200 mg. ○ = bupivacaine with adrenaline 1:200000 200 mg; —— = mean. Dashed line represents lower limit of concentration range at which toxic effects might be anticipated.

described toxic symptoms of a minor nature at an arterial concentration of 1.5–2.0 µg ml^{-1}. Depending on various factors, such as speed of infusion and site of injection, arterial concentrations may be 10–20% greater than venous concentration (Moore et al., 1976).

A recent review (Reynolds, 1987) contained a compilation of data from various sources which indicated that mild toxicity may occur at plasma concentrations of 1.6–2 µg ml^{-1}, with risk of serious toxicity at 2.3–5 µg ml^{-1}.

In this study the mean venous, measured plasma concentration never exceeded 2 µg ml^{-1} (2.5 µg ml^{-1} arterial, derived using a correction factor of 25%). In the steady state achieved during the later part of the study, this correction factor is possibly excessive. The scattergram (fig. 4) demonstrates that 11 individual measurements, all in the plain bupivacaine group, lie within the 2.3–5.0 µg ml^{-1} band in which major toxic effects might be anticipated. No measurement in the bupivacaine–adrenaline group exceeded 1.5 µg ml^{-1} (venous).

Adrenaline is known to decrease peak plasma concentration after all common nerve blocks (Wildsmith et al., 1977), but does not always prolong time to peak concentration (Tucker, 1986). This study confirms the finding of decreased peak plasma concentration, but also demonstrates a delay in reaching peak concentration.

Tucker (1986), using 2 µg ml^{-1} as a conservative estimate of safe plasma bupivacaine concentration together with data on peak concentration after various blocks, has calculated that accurate injection of much greater doses than 2 µg kg^{-1} should not exceed the toxic threshold. The results of this study support this calculation, in that the mean dose administered (3.3 mg kg^{-1}) did not result in mean venous plasma concentrations of more than 2 µg kg^{-1}, nor did any patient exhibit signs of toxicity.

Toxicity is related to the concentration of the drug which is free and active in the plasma. Bupivacaine has been shown to be highly protein bound: 90% at concentrations up to 5 µg ml^{-1} in *in vivo* experiments (Tucker and Mather, 1975).

The part played by protein binding in the *in vivo* situation has not been studied in detail, and more information is required on the free concentrations of bupivacaine occurring after nerve blocks. It would, however, seem prudent to use adrenaline-containing solutions when large volumes of drugs are required to complete a specific nerve block, in order to reduce the peak plasma concentration and minimize the risk of toxicity.

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COMPARISON OF THE INDUCTION CHARACTERISTICS OF THIOPENTONE AND PROPOFOL IN CHILDREN

G. PURCELL-JONES, A. YATES, J. R. BAKER AND I. G. JAMES

SUMMARY

The induction characteristics of propofol 2.0–2.5 mg kg^{-1} were compared with those of thiopentone 4–5 mg kg^{-1} in 60 fit children aged between 3 and 16 yr. All patients received i.m. premedication with papaveretum 0.4 mg kg^{-1} (maximum dose 15 mg) and hyoscine 0.008 mg kg^{-1} (maximum dose 0.3 mg). Seven children (24%) complained of pain after injection with propofol, compared with three (10%) after thiopentone. No child in either group complained of severe pain. Excitatory effects were observed in 10 children (33%) receiving propofol as opposed to five children (16%) after thiopentone, but these were transient and minor and all occurred after completion of injection. Apnoea lasting longer than 30 s occurred in only four children (13%) in each group despite the use of opioid premedication. The mean duration of apnoea was similar in both groups. Propofol caused greater decreases in arterial pressures (systolic, diastolic, mean) than thiopentone, but only the difference in systolic arterial pressure achieved significance. There was a significant difference in heart rate, which did not change after propofol, but increased with thiopentone. The overall quality of induction was assessed as being good in all children receiving thiopentone compared with 20 (66%) of those receiving propofol.

The withdrawal of Althesin and propanidid, and the high incidence of pain associated with the injection of methohexitone and etomidate, has left thiopentone as the most suitable i.v. induction agent for children. Propofol (2,6 di-isopropyl phenol) in an emulsion formulation has been used successfully in adults (Cummings et al., 1984; Fahy, van Mourik and Utting, 1985; Rolly and Versichelen, 1985) and has been shown to be a rapidly-acting induction agent with a short duration of action. There is a low incidence of pain when it is injected via forearm or antecubital fossa veins in adults (Cummings and Spence, 1985; McCulloch and Lees, 1985). These findings suggest that propofol may be a suitable induction agent for paediatric anaesthesia. We report a comparison of the characteristics of propofol 2.0–2.5 mg kg^{-1} with those of thiopentone 4–5 mg kg^{-1} for induction of anaesthesia in children.

PATIENTS AND METHODS

Sixty children aged between 3 and 16 yr were studied after hospital ethics committee approval and informed parental consent had been obtained. All patients were ASA I or II, and were undergoing a variety of surgical procedures. Exclusion criteria included obesity, known allergy to the trial drugs or their constituents, a history of previous adverse experience to general anaesthesia and the presence of hepatic, renal, haematological or metabolic disease and psychomotor retardation.

All patients were premedicated with papaveretum 0.4 mg kg^{-1} (maximum dose 15 mg) and hyoscine 0.008 mg kg^{-1} (maximum dose 0.3 mg) given i.m. 90 min before operation. On arrival of the patient in the anaesthetic room, systolic, diastolic and mean arterial pressures and heart rate were recorded using an automatic arterial pressure recorder (Dinamap, Critikon Limited). A 23-guage "Butterfly" needle (Abbott) was inserted to a vein in the antecubital fossa and

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G. PURCELL-JONES,† B.SC.(HON.), M.R.C.P., F.F.A.R.C.S.; A. YATES, M.B., B.S., F.F.A.R.C.S.; J. R. BAKER, B.SC.(HON.), M.B., CH.B., F.F.A.R C.S., I. G. JAMES, M.B., CH.B., F.F.A.R.C.S.; Department of Anaesthesia, The Hospital for Sick Children, Great Ormond Street, London WC1N 3JH Accepted for Publication · April 19, 1987.

† Present address, for correspondence: Department of Anaesthesia, St Thomas' Hospital, Lambeth Palace Road, London SE1 7EH.

flushed with sterile water to confirm correct positioning. The injection site was shielded from an independent assessor using a surgical drape, in order that he could remain unaware of the particular induction agent administered. A single dose of propofol 2.0–2.5 mg kg^{-1} or thiopentone 4–5 mg kg^{-1}, depending on random allocation, was injected over approximately 30 s. The dose was titrated to effect within the predetermined dose limits, using loss of eyelash reflex and acceptance of a face mask as the end-point. No other drugs were injected to the vein used for induction. If there was no spontaneous complaint within 10 s of commencement of injection, the child was asked if the arm was comfortable. If present, pain on injection was assessed as mild, moderate or severe, and any other sensations at the injection site or excitatory phenomena were noted. The induction time and dose, and presence and duration of apnoea were recorded. An observation period of 10 min followed, during which anaesthesia was maintained with 33 % oxygen, 66 % nitrous oxide and 1.5 % halothane. Systolic, diastolic and mean arterial pressures and heart rate were measured at 2-min intervals during this period and any other side effects noted. All objective measurements and observations were made by the independent assessor, who then made an overall subjective assessment which was recorded as good, adequate or poor, taking into account the number and severity of complications that occurred. The vein used for injection was inspected immediately following surgery and after 24 h, and the presence and severity of any thrombosis or phlebitis was recorded. In analysing the data, Students' t test and χ^2 with Yates' correction for small numbers were used, where appropriate.

TABLE I. *Characteristics of patients (mean (SEM))*

	Thiopentone	Propofol
n	30	30
Age (yr)		
Mean	7.53 (0.58)	6.46 (0.52)
Range	3–16	3–14
Weight (kg)		
Mean	26.16 (1.81)	23.32 (1.91)
Range	14.0–53.0	13.0–56.6
Sex (M/F)	17/13	19/11

TABLE II. *Incidence of pain on injection (antecubital fossa) (number (%))*

	n	Pain			Other sensation	Total
		Mild	Moderate	Severe		
Thiopentone	30	2 (7 %)	1 (3 %)	0 (0 %)	1 (3 %)	4 (13 %)
Propofol	30	2 (7 %)	5 (17 %)	0 (0 %)	2 (7 %)	9 (31 %)

TABLE III. *Induction doses and times (mean, SD or range)*

	Thiopentone	Propofol
Induction dose (mg kg^{-1})	4.73 (±0.32)	2.32 (±0.21)
Induction time (s)	29 (±3.44) 25–35	31 (±8.31) 18–60

TABLE IV. *Incidence of excitatory effects after induction of anaesthesia (number (%))*

	n	Spontaneous movements	Tremor	Total
Thiopentone 4–5 mg kg^{-1}	30	4 (13 %)	1 (3 %)	5 (16 %)
Propofol 2.0–2.5 mg kg^{-1}	30	10 (33 %)	0 (0 %)	10 (33 %)

RESULTS

The ages, weights and sex of the patients were similar in both groups and are shown in table I. There were more male than female patients in both groups.

The incidence of pain and other sensations (coldness and tingling) on injection is shown in table II. The total incidence of pain was greater in the group receiving propofol (24 %) than in that receiving thiopentone (10 %), but this did not reach statistical significance. No patients complained of severe pain in either group.

The mean induction doses of both agents are shown in table III. Anaesthesia was induced in all patients, but the induction time was prolonged in two patients receiving propofol. Both patients made semi-purposeful movements after an initial attempt to position the face mask following the loss of the eyelash reflex. In these patients, induction times were 45 and 60 s. The mean (SD) and range of induction times for both groups are shown in table III. There is no statistically significant difference between the groups.

The number of patients demonstrating spon-

TABLE V. *Apnoea*

	n	Range	Mean duration (s)	Duration > 30 s
Thiopentone 4–5 mg kg^{-1}	30	15–65	32.5 (±16.1)	4 (13%)
Propofol 2.0–2.5 mg kg^{-1}	30	10–55	25.3 (±16.36)	4 (13%)

TABLE VI. *Mean values for systolic, diastolic and mean arterial pressures (mm Hg) and heart rate (beat min^{-1}) after induction with thiopentone (T) or propofol (P)*

	Systolic arterial pressure		Diastolic arterial pressure		Mean arterial pressure		Heart rate	
Time (min)	T	P	T	P	T	P	T	P
Before induction								
0	116	111	65	57	83	77	93	91
After induction								
2	111	95	59	48	78	66	102	89
4	97	89	47	40	68	59	83	76
6	92	88	45	39	63	58	75	73
8	93	87	44	39	64	57	74	70
10	94	87	46	40	64	57	74	68

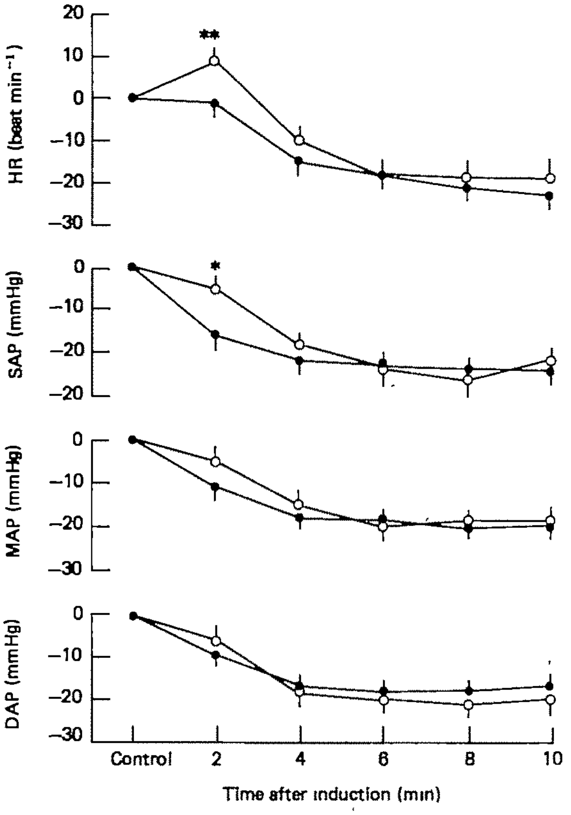

FIG. 1. Changes (mean, SEM) from baseline of heart rate and systolic, mean and diastolic arterial pressures following inductions of anaesthesia with propofol 2.5 mg kg^{-1} (●) and thiopentone 4–5 mg kg^{-1} (○) *$P < 0.05$; **$P < 0.02$.

TABLE VII. *Quality of induction*

	Poor	Adequate	Good
Thiopentone	0	0	30
Propofol	4	6	20

taneous movements and excitatory phenomena are shown in table IV. The incidence of spontaneous movement was greater in the propofol group (33%) than in the thiopentone group (13%), but this failed to achieve statistical significance. In all instances the movements were short-lived and none was considered troublesome. There was no hypertonus, hiccup or masseter spasm in any patient. One patient who received propofol developed laryngospasm, followed by vomiting, 2 min after commencing induction. This patient recovered, without further complications, following pharyngeal suction and oxygen. Anaesthesia was discontinued and the patient was withdrawn from the trial from that point. No data from this patient are included beyond the point at which he vomited.

Apnoea of greater than 30 s duration occurred in four (13%) patients in each group; details are shown in table V.

Systolic, diastolic and mean arterial pressures and heart rate are detailed in table VI. The variations in these variables from the baseline are illustrated in figure 1. The initial decreases in all the arterial pressures were consistently greater with propofol, but only the difference in systolic pressure reached statistical significance ($P < 0.05$) and that only at 2 min after induction. The decreases in diastolic pressure were similar in both groups and the difference in the mean arterial pressures is thus attributable to the significant decrease in the systolic pressure caused by propofol. The heart rate did not increase in the propofol group, as it did with thiopentone, and a significant difference was seen at 2 min after induction ($P < 0.02$).

The overall quality of induction was assessed as good in all patients when thiopentone was used, but this was not the case with propofol (table VII). The four children in whom induction was assessed as "poor" suffered moderate pain on injection, combined with both apnoea and mild involuntary movements. The six patients in whom induction was "adequate" complained of mild pain on injection associated with either apnoea or involuntary movements. Single minor side effects occurred during some "good" inductions, but were not severe enough to interfere with the overall quality. When "adequate" and "poor" inductions were pooled and compared with "good" inductions, using χ^2 with Yates' correction, a significant difference was found ($P < 0.01$) between the quality of induction with thiopentone and propofol. However, if clinically acceptable inductions (good and adequate) were compared with clinically unacceptable inductions (poor), the difference failed to reach statistical significance.

There were no significant venous sequelae within 24 h of induction. One patient in each group developed a transient phlebitis which was tender to touch 24 h after induction. This resolved within a further 24-h period. Neither of these patients experienced pain on induction.

DISCUSSION

The reported induction dose requirements with the emulsion formulation of propofol are varied. In non-premedicated adults, a range of 2.0–2.5 mg kg^{-1} was necessary (Cummings et al., 1984; Fahy, van Mourik and Utting, 1985; Rolly et al., 1985), whereas in premedicated adults a range of 1.5–2.0 mg kg^{-1} has been reported as satisfactory (Rolly and Versichelen, 1985). However, in a preliminary study of premedicated children, a dose of 2.0 mg kg^{-1} was not always sufficient for an acceptable induction (Purcell-Jones and James, 1985). Therefore, we chose the dose of 2.0–2.5 mg kg^{-1} for this study. Despite this larger induction dose and the relatively heavy premedication that is routinely used in this hospital, two children receiving propofol moved semi-purposefully in response to the placement of a facemask, following the loss of eyelash reflex. These two patients received propofol 2.22 and 2.52 mg kg^{-1}. No such problems occurred in the thiopentone group. However, this may in part be attributable to the difficulty in establishing an end-point for induction when using propofol. The abolition of the eyelash reflex is frequently used to establish this point and, when thiopentone is used, is accepted as indicating a reasonably constant level of central nervous system depression (Henshaw et al., 1980). This would appear not to be the case with propofol, as the application of a facemask following loss of verbal contact and eyelash reflex often stimulates spontaneous movements (Cummings et al., 1984; Purcell-Jones and James, 1985). Indeed, both children displaying semi-purposeful movements accepted a facemask within 60 s of commencement of induction without further increments of propofol. Although these two patients received 2.22 and 2.52 mg kg^{-1} of propofol, this was thought to be insufficient. Increased dose requirements have been noted in children compared with adults when using etomidate, Althesin and thiopentone (Keep and Manford, 1974; Kay, 1976; Duncan et al., 1984). This would also appear to be the case with propofol.

Between 12% and 37% of adults have been reported to develop spontaneous movements following propofol. Our observation of spontaneous movements in 33% of cases is similar to that reported by Fahy, van Mourik and Utting (1985) in premedicated adults and compares favourably with the 65% incidence of spontaneous movements found in children using a small (2.0-mg kg^{-1}) dose of propofol (Purcell-Jones and James, 1985). The number of patients who developed spontaneous movements was greater in the propofol group than in those receiving thiopentone. However, all of these movements were minor, occurred after completion of injection and were of short duration, lasting no longer than 30 s. Therefore, it would seem that there is no risk of extravasation on injection or interference with surgery as a result of sudden movement. The one notable exception was the child who vomited and developed laryngospasm 2 min after induction with propofol. He was thought to have regurgitated passively under light anaesthesia and consequently developed laryngospasm. He made a complete recovery without clinical or radiological evidence of aspiration. This complication was reported to the Committee for the Safety of Medicines.

The use of a fat emulsion as a vehicle for diazepam and propofol has reduced the incidence of pain on injection in adults (Von Dardel, Melbius and Mossberg, 1976; Von Dardel et al., 1983; Cummings et al., 1984). The Cremophor formulation of propofol was never used in children and direct comparison between the two formulations is not possible. Using the emulsion formulation, we have found a 24% incidence of pain using antecubital fossa veins, compared with

10% with thiopentone. Although none were considered to be severe, these findings contrast markedly with the low incidence of pain that was found in adults using antecubital fossa veins and the emulsion formulation of propofol (2.5–12%), or thiopentone (0%) (Kawar and Dundee, 1982; McCulloch and Lees, 1985; Wells, 1985). The incidence of pain on injection in adults is higher when the smaller veins on the dorsum of the hand are used (Kawar and Dundee, 1982; McCulloch and Lees, 1985; Mackenzie and Grant, 1985). We would expect this also to be the case with children, which would be quite unacceptable. Although pretreatment with lignocaine has been shown to reduce the incidence of pain when propofol is injected to the dorsal hand veins in adults (McCulloch and Lees, 1985), we do not feel that it would be ethical to attempt a similar controlled trial using hand veins in children. Certainly, Kay (1976) found that the addition of lignocaine to etomidate given to children did not affect the incidence of pain. We would recommend that the dorsum of the hand be avoided when using propofol in young children.

Transient apnoea occurred in 40% of the patients with both drugs, but lasted longer than 30 s in only four (13%) in each group. It did not prove to be a problem in either group and was never prolonged to the point where it prevented continuation of induction with a gaseous agent. That the incidence and duration of apnoea were almost identical for both drugs reflects on the relatively heavy opioid premedication. It is difficult to compare these findings with adult studies because the reported incidence of apnoea varies from 12 to 100% (Nightingale et al., 1984; Wells, 1985). Fahy, van Mourik and Utting (1985), using a technique similar to that utilized in this study, reported a higher incidence of apnoea with both thiopentone and propofol than we have found. Opioid premedication in adults reduces the induction dose of propofol at the expense of an increased incidence of marked respiratory depression in up to 25% of patients (Briggs et al., 1982). No child in this study developed marked respiratory depression despite the use of opioid premedication.

Both drugs produced significant decreases in systolic, mean and diastolic arterial pressures compared with preinduction base lines. The reduction in all of these variables was initially greater in the propofol group, but there was no statistical difference after 4 min. The decrease in systolic arterial pressure (20%) compares favourably with that (30%) reported in adults by Grounds and co-workers (1985) and regarded by them as acceptable. It has been suggested that a decrease in systemic vascular resistance, with a greater decrease in diastolic rather than systolic pressure, occurs with propofol (Fahy, van Mourik and Utting, 1985; Grounds et al., 1985). This study does not support these findings since the decreases in systolic pressure were greater than those in diastolic pressure in both the propofol and thiopentone groups. However, we can confirm the absence of an increase in heart rate following propofol (Prys-Roberts et al., 1983; Cummings et al., 1984; Grounds et al., 1985). Although the cardiac output following propofol in adults is not significantly reduced when compared with thiopentone (Grounds et al., 1985), more detailed haemodynamic studies need to be undertaken in children.

The results of this study indicate that propofol is an effective induction agent in fit children. It would seem that premedicated children need larger induction doses than adults, as even 2.5 mg kg^{-1} is insufficient in some cases. The incidence of spontaneous movements and pain on injection, as well as the decreases in arterial pressure, are greater when using propofol than with thiopentone. An overall subjective blind assessment of the quality of induction indicated that thiopentone was a better induction agent than propofol. The failure to demonstrate statistical significance in the differences in five of the seven objective variables studied was probably the result of the small number of children included in the study. Further investigations are needed to find means of reducing the pain on injection and to assess more fully the haemodynamic changes associated with the use of propofol for induction of anaesthesia in children.

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PHARMACOKINETICS OF ALFENTANIL IN CHILDREN UNDERGOING SURGERY

P. ROURE, N. JEAN, A.-C. LECLERC, N. CABANEL, J.-C. LEVRON AND P. DUVALDESTIN

SUMMARY

Alfentanil pharmacokinetics and protein binding were detemined in 20 children aged 10 months–6.5 yr. The data were compared with those from 10 adult patients. Eighteen children received a single i.v. dose of alfentanil 20 $\mu g\ kg^{-1}$. The apparent volume of distribution (V^{β}) did not differ between the two groups. The degree of plasma protein binding was also similar in children and adults with mean free fractions of 11.5 ± 0.9% (± SD) and 11.8 ± 3.9%, respectively. There were marked differences in the elimination half-life of alfentanil (63 ± 24 min in children; 95 ± 20 min in adults ($P < 0.001$)) and plasma clearance of alfentanil (11.1 ± 3.9 ml $min^{-1}\ kg^{-1}$ in children and 5.9 ± 1.6 ml $min^{-1}\ kg^{-1}$ in adults ($P < 0.001$)).

Alfentanil has a short duration of action in adults as a result of its short elimination half-life and moderate lipid solubility (Stanski and Hug, 1982). A short acting analgesic may be particularly useful in paediatric anaesthesia as the duration of surgery may be short and a high proportion of patients may be ambulatory. In the present study, the pharmacokinetics of alfentanil were measured in children undergoing orthopaedic surgery under general anaesthesia.

PATIENTS AND METHODS

Twenty children undergoing elective orthopaedic surgery were studied after ethics committee approval and parental consent. Their ages ranged from 10 to 78 months. All had normal hepatic and renal function. Premedication consisted of phenobarbitone 30–50 mg or diazepam 3–6 mg, and hyoscine 0.125–0.250 mg i.m. Anaesthesia was induced with thiopentone 6–8 mg kg^{-1} and droperidol 0.1 mg kg^{-1}. Pancuronium 0.05–0.07 mg kg^{-1} was given to facilitate tracheal intubation. Anaesthesia was maintained with 60% nitrous oxide in oxygen delivered by controlled ventilation. A single bolus dose of alfentanil 20 $\mu g\ kg^{-1}$ was administered in 18 patients. In two patients the dose of alfentanil was 50 $\mu g\ kg^{-1}$. If analgesia was inadequate, fentanyl in repeated doses of 10 μg was administered.

Ten adult patients (mean age 55 ± SD 11 yr; weight 65 ± 13 kg) undergoing elective peripheral surgery, and in whom a similar technique of anaesthesia was used, were studied also. After induction of anaesthesia, a bolus dose of 50 $\mu g\ kg^{-1}$ of alfentanil was administered to all the adult patients.

Venous blood samples (2 ml) were obtained before and 5, 10, 15, 30, 45, 60, 90, 120, 180, 240 and 300 min after alfentanil administration. Alfentanil plasma concentrations were measured by radioimmunoassay with a sensitivity of 0.1 ng ml^{-1} (Michiels, Hendriks and Heykants, 1983). It was verified that the antibody directed to alfentanil failed to bind fentanyl to any extent (Michiels, Hendriks and Heykants, 1983).

The free fraction (unbound fraction) of alfentanil was measured by equilibrium dialysis at 37 °C, using purified tritium-labelled alfentanil at two concentrations (50 and 500 ng ml^{-1}) and using plasma collected from each patient before surgery. An equilibrium dialyser (Dianorm, Dia-

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Pascal Roure, M.D.; Philippe Duvaldestin, M.D., Département d'Anesthésie, Hôpital Ambroise Paré, 92104 Boulogne Billancourt cedex, France. Nadine Jean, M.D.; Anne-Claire Leclerc, M.D.; Nicole Cabanel, M.D.; Département d'Anesthésie, Hôpital Raymond Poincaré, 92380 Garches, France. Jean-Claude Levron, Ph.D.; Laboratoires Janssen Lebrun 93300 Aubervilliers, France. Accepted for Publication: February 9, 1987.

Correspondence to P.D.

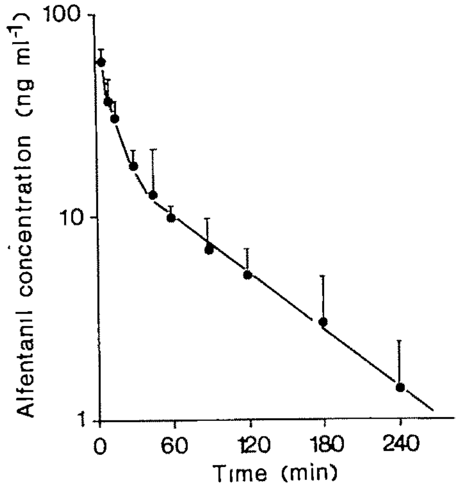

FIG. 1. Mean (±SD) alfentanil plasma concentrations in 18 children who received alfentanil 20 µg kg^{-1} i.v.

chema AG, Rüschlikon, Switzerland) composed of 1.3-ml Teflon cells and of dialysis membranes (Spectrapor 2, Spectrum, Los Angeles, California) was used. Plasma samples of 1 ml, to which the desired concentration of alfentanil had been added, were dialysed against 1 ml of 0.067-mol litre^{-1} phosphate buffer, pH 7.3. The cells were rotated at 20 rev min^{-1} in a drive system in a thermostatically-controlled water bath at 37 °C. A dialysis time of 4 h was chosen.

A model-independent approach using the total alfentanil plasma concentration at each time was used to calculate the pharmacokinetic values. Clearance (*Cl*) was calculated by dividing the dose by the area under the curve as determined by the linear trapezoidal rule. The terminal elimination half-life ($T_{\frac{1}{2}}^{\beta}$) was calculated by linear regression of the log-plasma concentration *v*. time data after the distribution phase. The total apparent volume of distribution (V^{β}) was calculated from the following formula:

$$V^{\beta} = T_{\frac{1}{2}}^{\beta} \times Cl \times 1.44$$

Statistical analysis was by Student's *t* test.

RESULTS

The duration of anaesthesia in children varied from 45 to 165 min. Additional doses of fentanyl were administered in nine patients. Two patients (Nos 8 and 17) received blood transfusion. Among the children, there was no correlation between age and the plasma concentration of alfentanil at any sampling time. The mean plasma alfentanil concentrations in the 18 patients receiving alfentanil 20 µg kg^{-1} are shown in figure 1. The plasma concentration curve was bi-exponential in all patients. The pharmacokinetic values are listed in table I. In the two patients (Nos 6 and 13) receiving the higher dose of

TABLE I. *Age and individual pharmacokinetic values of alfentanil in 20 children*

Patient No.	Dose of alfentanil (µg kg^{-1})	Age (months)	$T_{\frac{1}{2}}^{\beta}$ (min)	*Cl* (ml min^{-1} kg^{-1})	V^{β} (litre kg^{-1})
1	20	10	53	14.2	1.9
2	20	10	53	11.5	0.88
3	20	11	56	9.7	0.79
4	20	21	39	20.7	1.17
5	20	21	56	10.7	0.88
6	50	23	60	11.8	1.02
7	20	24	49	12.7	0.89
8	20	24	48	7.6	0.53
9	20	27	53	13.4	1.03
10	20	27	53	8.1	0.63
11	20	28	62	9.8	0.88
12	20	31	66	10.5	1.01
13	50	33	59	13.3	1.13
14	20	41	77	13.4	1.50
15	20	42	61	12.1	1.06
16	20	50	53	7.7	0.59
17	20	50	156	17.0	3.82
18	20	60	53	6.0	0.46
19	20	60	79	8.6	0.98
20	20	78	71	3.2	0.33

TABLE II. *Mean ($\pm SD$) pharmacokinetic values for alfentanil in adult and paediatric patients undergoing elective surgery under general anaesthesia.* *$P < 0.001$ v. *adult patients*

	$T_{\frac{1}{2}}^{\beta}$ (min)	Cl (ml min^{-1} kg^{-1})	V^{β} (litre kg^{-1})	Free fraction (%)
Adult patients	95	5.9	0.82	11.8
($n = 10$)	±20	±1.6	±0.30	±3.9
Paediatric patients	63*	11.1*	1.03	11.5
($n = 20$)	±24	±3.9	±0.71	±0.9

alfentanil (50 µg kg^{-1}), the pharmacokinetic values did not differ from those in the other children. No correlation was observed between age and any of the pharmacokinetic values in children. The elimination half-life was significantly ($P < 0.001$) shorter in children than in adults (table II). This change was explained by the higher clearance in children, whereas the volume of distribution did not differ between the two groups. The alfentanil free fraction in plasma averaged 11.5±0.9% and 10.2±1.7% in children when tritiated alfentanil was used at concentrations of 50 and 500 ng ml^{-1}, respectively. These values were not significantly different from the values of 11.8±3.9% and 11.5±2.9% obtained in adults.

DISCUSSION

In the present study, most children received a small dose of alfentanil 20 µg kg^{-1}, compared with 50 µg kg^{-1} in adults, because we were reluctant to administer a higher dose until we had studied the pharmacological properties of alfentanil in children. This difference in dose may lead to misinterpretation if the pharmacokinetics of alfentanil are not linear over this dose range. However, there is no convincing evidence for a dose-dependent clearance of alfentanil in normal subjects (Mather, 1983) and no differences were observed in the pharmacokinetics of alfentanil between doses of 50 and 125 µg kg^{-1} (Bovill et al., 1982).

In children the elimination half-life of alfentanil was shorter as a result of an increase of 90% in its plasma clearance. An increase in the clearance of many drugs during childhood has been observed (Morselli, Franco-Morselli and Bossi, 1980) and may be explained by enhanced drug metabolism for drugs such as anticonvulsants (Morselli, 1976), theophylline (Rane and Wilson, 1976) and thiopentone (Sorbo, Hudson and Loomis, 1984), which are oxidized by the mono-oxygenase system and have a low hepatic extraction coefficient. Therefore, the increased plasma clearance of these drugs during childhood is explained by an increase in hepatic microsomal enzyme activity which ends at the age of 3 yr (Morselli, Franco-Morselli and Bossi, 1980). However, an increase in biotransformation alone probably does not explain the increase in the clearance of alfentanil observed in children. Owing to the intermediate value of the hepatic extraction coefficient of alfentanil (0.4 and 0.7) (Bovill et al., 1982; Ferrier et al., 1985), its clearance is dependent upon both drug metabolizing capacity and hepatic blood flow. There is also an increase in the hepatic blood flow in children which is related to the increase in both the liver weight over body weight ratio (Yaffe and Juchau, 1974) and in the cardiac index. Therefore, the increased hepatic blood flow probably contributes also to the increased clearance of alfentanil. The extent of protein binding of alfentanil might also influence the plasma clearance of alfentanil; however, the alfentanil free fraction was similar in the children and the adults.

Preliminary results concerning two other pharmacokinetic studies of alfentanil also indicate a shortening in the elimination half-life of alfentanil in children receiving enflurane (Meistelman et al., 1984) or halothane (Sale et al., 1986). In both studies, however, the decrease in the elimination half-life was explained by a reduced volume of distribution despite the absence of a control group of adults. In addition, the use of halogenated volatile anaesthetics which are known to diminish hepatic blood flow (Meistelman et al., 1984; Sale et al., 1986) may counter the effect of age on alfentanil plasma clearance. In the elderly, alfentanil clearance is decreased (Helmers et al., 1984).

The pharmacokinetics of other opioid analgesics have been studied in children. Dahlström and colleagues (1979) found no differences in the pharmacokinetics of morphine in paediatric patients aged 1–15 yr. In neonates, an increased volume of distribution of fentanyl was observed (Johnson et al., 1984; Koehntop et al., 1986), whereas the elimination half-life was prolonged only in those undergoing abdominal surgery combined with increased abdominal pressure after surgery (Koehntop et al., 1986). An increase in the clearance of fentanyl was observed in children (Singleton, Rosen and Fisher, 1984) or in some category of children at least, between the ages of 1 month and 1 yr (Johnson et al., 1984).

Because of the rapid transfer of alfentanil across the blood–brain barrier (Stanski and Hug, 1982) it is expected that a close relationship exists between the plasma concentration and the effect of alfentanil. Therefore, the results of this study suggest that alfentanil will have a short duration of action in paediatric patients.

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CONTINUOUS EXTRADURAL ANAESTHESIA IN CHILDREN

Clinical and Haemodynamic Implications

I. MURAT, M. M. DELLEUR, C. ESTEVE, J. F. EGU, P. RAYNAUD AND C. SAINT-MAURICE

SUMMARY

This study reports the experience of a department of paediatric anaesthesia with 234 continuous extradural anaesthetics performed in 229 children over a 15-month period. Fifty-nine of the children were aged 0–2 yr, 71 were aged 2–8 yr and 104 were older than 8 yr. The surgical procedures lasted more than 60 min (mean 150 ± 10.6 min); all were carried out under light general anaesthesia. Technical procedure and difficulties are reported. The only local anaesthetic agent used was bupivacaine with or without adrenaline. Mean initial dosage was 0.75 ml kg^{-1} for children weighing less than 20 kg and 1 ml/10 cm of height for children taller than 100 cm. Using 0.25% bupivacaine mean times until a further injection were 92.0 ± 2.0 min for bupivacaine with adrenaline and 71.0 ± 2.5 min for bupivacaine without adrenaline ($P < 0.001$). A much longer duration of analgesia was found for younger children using the solution with adrenaline. A haemodynamic study was performed in 74 unpremedicated children (ASA I; aged 0–2 yr ($n = 15$), 2–8 yr ($n = 26$) and older than 8 yr ($n = 35$)). Before induction of anaesthesia, heart rate (HR) was significantly increased in the youngest children, but no significant change was found for systolic arterial pressure (SAP). After extradural anaesthesia with 0.25% bupivacaine with adrenaline 1:200000, minimal changes in HR or SAP occurred in children younger than 8 yr; in those older than 8 yr a significant decrease in both HR and SAP was observed. Changes in SAP were at their maximum 25 min after the extradural block and changes in HR were not statistically significant before the 25th min following injection of local anaesthetic. The catheter remained in place in 155 children for postoperative analgesia, mainly for the first 48 h.

Continuous extradural anaesthesia is used frequently in adults in combination with general anaesthesia for abdominal or orthopaedic surgery. The technique is of interest since it decreases the requirements for systemic analgesics and neuromuscular blocking drugs (the drugs which are responsible for ventilatory depression in the postoperative period) and can provide effective postoperative analgesia (Catley et al., 1985). In children, extradural block via the caudal route is often used for day-case surgery so as to decrease postoperative morbidity and provide satisfactory pain relief (Armitage, 1979; McGown, 1981). Continuous extradural blockade via the thoracic or lumbar routes is much less common in children because it requires considerable clinical experience and appropriate equipment.

This study describes the experiences of the Department of Paediatric Anaesthesia with continuous lumbar or thoracic extradural blockade. During a 15-month period, 234 continuous extradural anaesthetics were performed, 59 in children younger than 2 yr, 71 in children aged 2–8 yr and 104 in children older than 8 yr.

All information regarding the patients, surgical procedures, techniques, doses and haemodynamic data was collected prospectively and analysed by computer (Apple IIe).

PATIENTS AND METHODS

All extradural anaesthetics performed by the thoracic or lumbar approach before surgery are included in this study. All were carried out between June, 1984 and October, 1985. Informed

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I. MURAT, M.D.; M. M. DELLEUR, M.D.; C. ESTEVE, M.D.; J. F. EGU, M.D.; P. RAYNAUD, M.D.; C. SAINT-MAURICE, M.D.; Département d'Anesthésie-Réanimation Chirurgicale, Hôpital Saint-Vincent-de-Paul, 74, avenue Denfert-Rochereau, 75674 Paris Cédex 14, France.

Correspondence to I. M.

consent was obtained from the parents; the technique and its relevance were explained during the preoperative consultation. The study was approved by the ethics committee of the hospital. Indications for continuous extradural anaesthesia were: surgery lasting more than 60 min or the necessity for effective postoperative pain relief to facilitate nursing or physiotherapy. The children were either unpremedicated or premedicated with a benzodiazepine (either by mouth or *per rectum*). The lumbar or thoracic extradural space was punctured after the induction of general anaesthesia in all patients, and following intubation of the trachea in most patients. The extradural space was punctured in the lateral decubitus position with a Tuohy needle, 17-, 18-, 19- or 20-gauge according to the age of the child. The extradural space was identified using the loss of resistance technique with a syringe containing physiological saline. A 3-ml glass syringe was used for children weighing less than 10 kg, and a syringe of 5 or 10 ml for the other children. A catheter was inserted once the extradural space had been identified. Two types of catheter were used: for children less than 10 kg, a 24-gauge polyurethane catheter with a stylet and, for children of about 10 kg or more, a 20-gauge nylon catheter with a stylet. The 24-gauge catheter can be introduced through a 20-gauge needle, and the 20-gauge through a 17- or 18-gauge needle. Both catheters were graduated and no more than 2 or 3 cm was placed in the extradural space. In all patients the local anaesthetic used for the operative period was bupivacaine with or without adrenaline 1:200000. The concentrations used ranged between 0.25 and 0.5%. For children younger than 8 yr, we used only a solution of 0.25% bupivacaine. For older children, more concentrated solutions (0.37 or 0.5%) were used during surgery, either when abdominal wall relaxation was requested or for orthopaedic surgery of lower limbs. Bupivacaine without adrenaline was used for the initial patients studied but, when it became obvious that the addition of adrenaline was associated with a prolonged analgesic effect, use of the latter solution was preferred, except for children with cardiac abnormalities. The segmental level of the puncture was chosen according to the surgical procedure. A mean initial dose of bupivacaine 0.75 ml kg^{-1} was used for children weighing less than 20 kg and a dose of 1 ml/10 cm of height for children taller than 100 cm. Additional injections were performed either systematically according to the pharmacodynamic properties of the local anaesthetic used or when there were changes in arterial pressure (AP) or heart rate (HR). The volume of these subsequent injections was always one-half that of the initial injection. Before each injection or re-injection, aspiration was performed to ensure that no blood flowed back. A test dose of 0.25% bupivacaine 1–2 ml with adrenaline 1:200000 was given to each child, except for the first 50 patients. The total dose of local anaesthetic was then injected 3 min after the test dose if there was no significant change in heart rate or arterial pressure. The rate of injection depended on the size of the catheter. For the smallest (24-gauge) catheter, the speed of injection was very slow because of the high resistance of the small catheter.

A haemodynamic study was performed on some unpremedicated patients. All were free from cardiac or pulmonary disease and were taking no medication. In these patients, anaesthesia was induced either with an inhalation agent (halothane in most cases) or with an i.v. agent (thiopentone 5–10 mg kg^{-1}). In all patients the trachea was intubated after a single dose of vecuronium (80–100 μg kg^{-1}). None received opioids either as a premedication or for the induction of anaesthesia. All these children had the lungs ventilated mechanically in order to maintain $P\text{E}'_{CO_2}$ within physiological range (4–5 kPa). Haemodynamic data were obtained under nitrous oxide–enflurane anaesthesia with an inspiratory concentration of enflurane less than 1.5%.

Haemodynamic variables were monitored using an ECG monitor and an indirect monitor of arterial pressure (Dinamap). In all children, systolic arterial pressure (SAP) and heart rate (HR) were recorded before the induction of anaesthesia, 5 min before extradural puncture, 5, 10 and 25 min after the injection of the local anaesthetic, at skin incision and 15 min after skin incision. In all these children, the puncture was performed at L2–3 or L3–4 and the segmental level of analgesia ranged from T8 to T10. The levels of analgesia obtained were assessed during surgery and with greater precision at the end of the surgical procedure. All children received a standard infusion of 5% dextrose 7–10 ml kg^{-1} during the first 1 h of anaesthesia. None received any blood, modified gelatine solution or vasoactive drugs. Temperature was monitored and maintained between 36 and 37 °C. Haemodynamic data obtained in 10 children in whom puncture

TABLE I. *Details of patients and surgical procedures involved*

Age	*n*	Weight (kg)	Height (cm)	Orthopaedic surgery	*n*	Visceral surgery	*n*
2 days–2 yr	59	2–13.4	48–89	Club foot	11	Pull through	10
				Pelvic osteotomy	2	Genito-urinary procedures	29
						Nissen procedures	2
						Excision of tumour	5
2–8 yr	71	10–26	80–135	Club foot	13	Genito-urinary procedures	39
				Pelvic osteotomy	7	Pull through	5
				Various bone surgery	4	Excision of tumour	3
> 8 yr	104	14–85	108–180	Prothesis for Ewing sarcoma	21	Genito-urinary procedures	21
				Triple arthrodesis of the foot	18	Excision of tumour	3
				Pelvic osteotomy	6		
				Tenotomies	14		
				Various bone surgery	21		

TABLE II. *Time of the first reinjection of 0.25% bupivacaine, with or without adrenaline, according to age*

	0.25% Bupivacaine with adrenaline		0.25% Bupivacaine without adrenaline		Increased duration of analgesia with adrenaline	
Age (yr)	*n*	Time (min)	*n*	Time (min)	%	*P*
0–18	94	92.07 ± 2.0	31	71.01 ± 2.57	29.6	< 0.001
0–2	27	97.6 ± 4.56	15	66.3 ± 4.1	47	< 0.001
2–8	36	93.0 ± 3.12	8	74.4 ± 4.6	25	< 0.01
8–18	31	86.23 ± 3.16	8	76.7 ± 4.6	12	ns

had been performed between L3–4, were compared with those obtained in 10 children in whom puncture was performed at a dorsal interspace (between T7 and T11). Children were paired for age and weight. The local anaesthetic used in both groups was 0.25% bupivacaine with adrenaline. The level of analgesia in this latter group ranged from T4 to T6.

Postoperative analgesia

The catheter remained in place in most patients after surgery in order to allow the further administration of local anaesthetic or extradural opioids to provide postoperative analgesia as indicated. A bacterial filter of 22 µm was used in each case. Because of medico-legal reasons and the recent introduction of this technique, such additional administrations were performed only by an anaesthetist. These further injections were only performed if there were signs of pain, either as assessed by the nurses, parents and doctors in the youngest children, or as expressed by the child itself in those who were older. Any complications of the technique were followed up after surgery.

Statistical analysis

Statistical analyses were made by repeated analysis of variance. The paired Student's *t* test was used for observations in same patients and the unpaired Student's *t* test for comparison in different groups. *P* values of less than 0.05 were regarded as significant. Results are expressed as mean ± SEM.

RESULTS

Patients

Continuous extradural anaesthesia was performed on 234 occasions in 229 children: 59 in children aged 2 days to 2 yr, 71 in children aged 2–8 yr and 104 in children older than 8 yr. Physical characteristics of each group and the surgical procedures involved are summarized in table I. In children younger than 8 yr the surgery was mainly visceral (complex hypospadias repair, pull through for Hirschprung disease) and, less frequently, orthopaedic surgery (repair of club foot or pelvic osteotomy for congenital dislocation of the hip). In children older than 8 yr, surgery was mainly

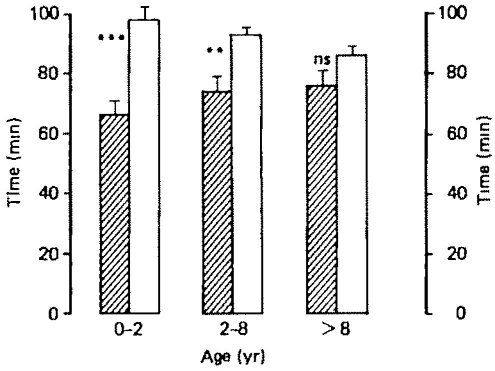

FIG. 1. Time of the first peroperative reinjection of 0.25% bupivacaine according to age and use of adrenaline 1:200000 (open columns) or bupivacaine without adrenaline (hatched columns). $^{**}P < 0.01$; $^{***}P < 0.001$.

orthopaedic (prosthesis for bone tumours or various arthrodesis or osteotomy).

Most children were ASA I or II. In this study, no regional anaesthesia was performed for emergency surgery. However, some of the children included in this study had major anaesthesia risks: neuromuscular disease in 36 (Duchenne myopathy in 30), adrenocortical insufficiency in four, severe respiratory failure in 10 (bronchopulmonary dysplasia or sequelae of poliomyelitis); 10 children had a history of allergic disease, eight had a congenital cardiac malformation, but were not in severe heart failure. Mean duration of the surgical procedure was 150 ± 10.6 min, and the mean duration of general anaesthesia 190 ± 9.8 min. Mean time between induction of anaesthesia and extradural puncture was 20 ± 3.2 min, and the mean time between injection of local anesthetic and skin incision was 25 ± 2.1 min.

Technical procedure

Extradural puncture was made through a low lumbar space in most patients: L3–4 in 139, L4–5 in 16. The other sites of puncture were lumbar (L1–2 in 21; L2–3 in 43) or thoracic (T7–8 in one; T8–9 in three; T9–10 in two; T10–11 in three; T11–12 in two; T12–L1 in four). All the difficulties associated with the insertion of the needle were found in the first 50 patients. Two attempts were made in 10 children and three attempts in three. The catheter was difficult to place in the extradural space in 10 children, but this technical problem was solved by advancing the needle for 1 or 2 mm in eight of the 10.

Drug and dose

Analgesia was sufficient in 224 children such that no systemic analgesics were required during the operative procedure. In the other 10, adequate analgesia was obtained after an additional injection of local anaesthetic.

The volume used for subsequent "top-up" injections was always one-half the initial volume. The time of the first additional injection depended on age, concentration of local anaesthetic used and

TABLE III. *Haemodynamic data (HR = heart rate (beat* min^{-1}*); SAP = systolic arterial pressure (mm Hg)) obtained in* 76 *unpremedicated children. Significant changes compared with pre-induction values using* t *test for paired samples*: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$ *Before induction of anaesthesia, heart rate decreased significantly with age* ($P < 0.001$)*, but no significant change was found for SAP*

Age (yr)	Before induction	5 min before blockade	Time after injection (min) 5	10	25	Skin incision	15 min after skin incision	*P*
<2 (*n* = 15)								
HR	127.8	128.9	126.0	127.0	123.4	120.7*	119.5*	ns
	±3.8	±5.8	±5.7	±5.4	±4.9	±5.0	±4.9	
SAP	100.3	97.0*	96.5	96.4	91.9*	95.0	90 7*	ns
	±4.6	±4.1	±4.1	±3.8	±3.2	±3.4	±4.2*	
2–8 (*n* = 26)								
HR	110.6	108.6	106.8	106.3	106.3	105.4	102.9	ns
	±3.3	±2.1	±2.7	±3.2	±3.6	±3.5	±3.2	
SAP	101.4	98.6	94.3*	94.1*	97.5	97.5	95.7	ns
	±3.3	±2.8	±2.8	±2.9	±2.7	±2.6	±2.6	
> 8 (*n* = 35)								
HR	98.7	99.1	97.2	94.5	89.3*	88.1**	86.1***	< 0.01
	±3.4	±3.0	±3.3	±3.4	±3.0	±2.9	±3.1	
SAP	108.5	100.3***	97.7***	94.3***	92.1***	92.7***	92.5***	< 0.001
	±2.4	±1.8	±2.0	±2.0	±1.9	±2.2	±1.8	

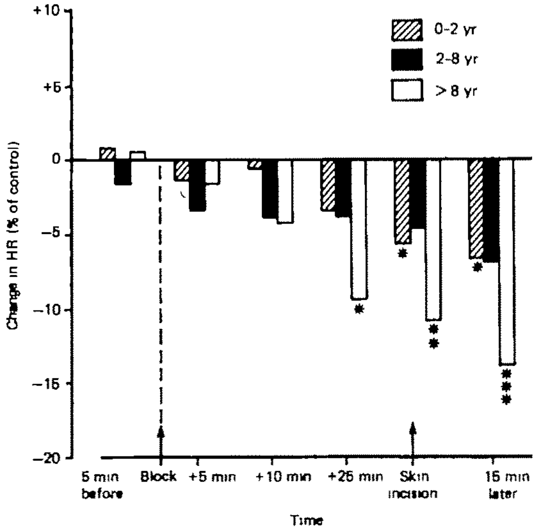

FIG. 2. Changes in heart rate expressed as percent of pre-induction values. Values were obtained 5 min before, and 5, 10 and 25 min after, extradural blockade (Block); at skin incision and 15 min after skin incision. Compared with pre-induction: $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$.

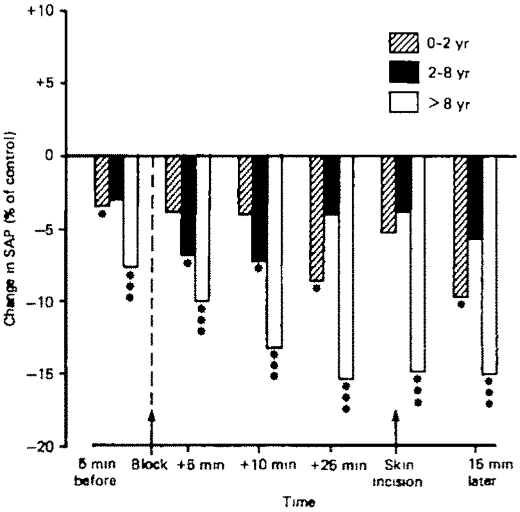

FIG. 3. Changes in SAP expressed as percent of pre-induction values. Details as for figure 2.

on the concomitant use of adrenaline. Bupivacaine 0.25% was the local anaesthetic used most frequently. Addition of adrenaline 1:200000 increased the duration of analgesia by 29.6% ($P < 0.001$) (table II). However, the increase in the duration of analgesia was less marked in older children than in younger ones. For children younger than 2 yr the mean duration of analgesia increased by 47% ($P < 0.001$), and for those aged 2–8 yr it increased by 25% ($P < 0.01$). An increase of 12% (not significant) was found in children older than 8 yr (fig. 1).

In children younger than 8 yr, 0.25% bupivacaine was the only anaesthetic used. In children older than 8 yr, 0.25%, 0.375% or 0.5% bupivacaine was used. The duration of anaesthesia was longer when using bupivacaine with adrenaline than when using bupivacaine without adrenaline (92.7±2.9 *v.* 77.3±3.9 min) ($P < 0.01$). Duration of anaesthesia was increased when using the more concentrated solutions (0.37% and 0.5%) when compared with the least concentrated (0.25%) (102.0±5.3 *v.* 86.2±3.2 min) ($P < 0.01$).

Haemodynamic studies

In 76 children (ASA I), haemodynamic data were recorded every 5 min; the children were divided into three groups according to age. Before the induction of general anaesthesia, heart rate (HR) was greater in the youngest children. The decrease in heart rate with age was significant ($P < 0.001$). No significant change was found for pre-induction systolic arterial pressure (SAP) between the groups (table III). The local anaesthetic used in all cases was 0.25% bupivacaine with adrenaline. In children younger than 2 yr, HR was significantly decreased at the time of skin incision (about 30 min after the extradural block) and at 15 min after incision. SAP decreased significantly after the induction of anaesthesia when compared with pre-induction values, and a moderate but significant decrease was found 25 min after extradural blockade and 15 min after skin incision (figs 2 and 3). In children aged between 2 and 8 yr, HR did not change at any time when compared with pre-induction values. SAP decreased significantly 5 min and 10 min after extradural blockade and thereafter returned to pre-induction values.

In children older than 8 yr there were significant decreases in HR ($P < 0.01$) and SAP ($P < 0.001$). When compared with pre-induction values, HR had decreased significantly 25 min after extradural blockade, at the time of skin incision and 15 min later. SAP decreased at each time when compared with pre-induction values. Maximum decrease was observed 25 min after extradural block. Haemodynamic data obtained in 10 children with a block up to T8–10 (puncture between L2 and L4) were matched with those obtained in 10 children of the same age and weight

TABLE IV. *Haemodynamic data obtained in two groups of 10 children matched for age and weight according to maximum level of blockade. Statistical analysis was by t test for paired data*

	Block up to T10–12 ($n = 10$)	Block up to T4–5 ($n = 10$)	P
Age (months)	34.6±0.8	35.1±1.0	ns
Weight (kg)	13.8±1.9	13.7±1.9	ns
Heart rate (beat min^{-1})			
Before induction	112.6±5.5	123.5±3.6	ns
5 min before blockade	117.0±5.2	122.9±6 3	ns
5 min after injection	109.5±5.8	126.3±7.0	ns
10 min after injection	108.1±6.1	123.7±7.6	ns
25 min after injection	109.5±5.7	119.2±7.0	ns
Skin incision	105.7±6.4	120.1±7.1	ns
15 min after skin incision	104.9±6.8	119.4±7.5	ns
Systolic AP (mm Hg)			
Before induction	109.0±4.7	105.3±6.7	ns
5 min before blockade	107.5±4.0	100.2±5.0	ns
5 min after injection	101.3±3.2	95.2±4.8	ns
10 min after injection	98.5±2.9	94.6±4.2	ns
25 min after injection	98.8±2.7	90.2±4.3	ns
Skin incision	99.4±2.7	92.3±3.1	ns
15 min after skin incision	100.0±3.5	85.3±3.7	< 0.02

with a block up to T4–5. No difference between groups was observed for both HR and SAP except for the last value of SAP obtained 15 min after skin incision (table IV). At this time, SAP was significantly lower in the high thoracic group.

Postoperative analgesia

The catheter remained in place in 155 children into the postoperative period for a mean of 35±31 h. In those children studied initially the catheter was removed systematically on the 2nd day after operation. Later in the study the catheter remained *in situ* for as long as top-up injections were required for postoperative analgesia. The catheter was then removed if no injection had been made during the past 18 h and if the child showed no signs of pain. No complications were observed except for a technical problem with the 24-gauge catheter when placed in the youngest children. A leak of local anaesthetic was noted, during reinjection, between the catheter and the bacterial filter. In these patients, the catheter was removed. This problem occurred in 10 of the first 20 children aged less than 2 yr and was resolved by changing the connection between catheter and bacterial filter. Except for this technical problem, no other complication was observed in regard to the maintenance of the catheter in the extradural space.

Complications

Except for failures caused by an insufficient initial dose, which are reported above, only two complications were observed during the 15 months of the study. The first was a dural puncture in an 8-yr-old child. The needle was removed and no other attempt made. General anaesthesia was used, and there was no headache in the postoperative period. This accidental puncture occurred in one of the first 20 patients and was the second attempt of one of the authors. The second complication was an accidental intravascular injection in a 14-yr-old child. Both puncture and insertion of the catheter were easy. Aspiration was carried out before injection and no blood was noticed. During the injection of 0.25% bupivacaine with adrenaline, changes in heart rate occurred with arrhythmia and supraventricular extrasystoles. The injection was stopped, and blood flowed back through the catheter when a further aspiration test was performed. The catheter was immediately removed and heart rate spontaneously returned to baseline in less than 60 s. General anaesthesia was successfully carried on without any additional problems.

DISCUSSION

Patients, techniques and indications

Continuous extradural anaesthesia was performed in children in order to reduce peroperative requirement of opioids and myoneural blockers and to provide complete per- and postoperative analgesia. This procedure is of particular interest for visceral surgery of long duration and for orthopaedic surgery, which is often very painful. Reducing or avoiding opioids and myoneural blocking drugs during surgery should decrease the incidence of postoperative respiratory depression—which is the major cause of postoperative death. That is especially true in young children, in whom the elimination half-life of most drugs is usually two or three times longer than in adults (Rowland and Tozer, 1980). Thus continuous extradural anaesthesia allows the anaesthetist to reduce indications for postoperative ventilation and allows rapid extubation of the trachea without risk. Most of the visceral procedures were genito-urinary procedures or pull through for Hirschsprung disease. In both, the extradural technique makes the nursing of young children easier and aids the removal of various catheters (Delleur et al., 1985). The puncture of the extradural space was always performed under general anaesthesia. The distance between skin and extradural space is very small in young children and absolute stillness is necessary to avoid accidental dural puncture (Schulte-Steinberg, 1980). The duration of the surgical procedure itself is another reason for using regional anaesthesia combined with general anaesthesia. The technical failures were all attributable to the inexperience of the anaesthetists and the percentage failures decreased dramatically with experience; currently, the technique is used routinely. However, in young children the resistance of the ligamentum flavum is weaker than in adults and the compliance of the extradural space is greater. Thus the use of a graduated needle with a short bevelled edge is recommended in addition to a glass test syringe of small volume. The smallest test volume had to be injected in order to avoid too large dilution of local anaesthetic. The lateral approach to the thoracic space also can be used (Meignier, Souron and LeNeel, 1983). This approach was not used in the present study. Ruston (1954, 1957) used the technique of the "hanging drop" to locate the extradural space. The loss of resistance technique used in this study is, however, perfectly acceptable even for young children. The introduction of the catheter was not linked with specific problems in children. However, a stylet is needed for the flexible polyurethane catheters, but the stylet should always be withdrawn before the extradural space is entered. In young children, polyurethane is a useful material: it is non-toxic, flexible and well tolerated. The catheters should have a terminal orifice and should be graduated so that one can be sure of the exact length of catheter inserted.

The mean recommended dose used in the present study was satisfactory and provided blockade of at least 10 segments. However, both volume and level of puncture had to be combined in order to use the minimal drug volume appropriate for the intended surgical procedure. For example, for pull-through operations, our first attempts were performed at L3–4, but we now prefer L1–2 level in order to reduce dosage.

No motor blockade was observed at the end of surgery when using a solution of 0.25% bupivacaine. No lateralization of analgesia was evident. If required, analgesia of the sacral roots was always satisfactory. Anatomical differences between children and adults can explain these results. The smaller diameter of the sacral roots and poor myelinization, when compared with adults, can explain the success in sacral blockade by extradural lumbar approach especially in young children. The contents of the extradural space obviously differ from those of adult patients. The extradural fat of the newborn and the young child has a gelatinous, spongy appearance, with distinct spaces between the individual fat lobules. In contrast, the lobules are more densely packed and interrupted by strands of fibre in adults. Thus, the extradural fat offers less of an obstacle to longitudinal spread of injected solutions in children (Schulte-Steinberg, 1980).

The time of the first additional injection depended on age, on the concentration of local anaesthetic used and on the concomitant use of adrenaline. The decease in mean duration of analgesia with age was expected according to changes in pharmacokinetic values with age (Eyres et al., 1978). This was not observed in the present study for bupivacaine without adrenaline because the number of patients in this group was small. In contrast, using bupivacaine with adrenaline, the duration of analgesia was significantly longer for children younger than 2 yr when compared with those older than 8 yr ($P < 0.05$).

No other difference between the groups was significant. The use of adrenaline was associated with an increase in the duration of analgesia in all children. However, a much greater increase in the duration of the analgesia was found in the youngest children. Similar results were reported recently by Warner and colleagues (1985) using bupivacaine by the caudal route for postoperative pain relief. Thus the prolongation of analgesia observed is an important reason for recommending the use of a 1:200000 dilution of adrenaline with 0.25% bupivacaine in order to reduce the dose required for per- and postoperative analgesia. In children older than 8 yr an expected increase in mean duration of analgesia was observed with increasing concentration of local anaesthetic. Once more, the expected difference was observed using bupivacaine solution with adrenaline.

Haemodynamic study

The extradural injection of plain solutions of local anaesthetic agents in conscious adult patients is associated with minimal changes in haemodynamic variables if the segmental block obtained does not extend above T5 (Bonica, Berges and Morikawa, 1970). The vasodilatation observed in the blocked area is, in the main, compensated for by vasoconstriction in the unblocked area. However, these results could be modified by the concomitant use of general anaesthesia and by the addition of adrenaline. General anaesthesia, even light, interferes with the compensatory vasoconstriction in the upper part of the body (Stephen, Lees and Scott, 1969; German, Roberts and Prys-Roberts, 1979). The addition of adrenaline during extradural anaesthesia combined with general anaesthesia was studied by Scott and coworkers (1977) in adult patients. They observed decreases in arterial pressure and peripheral vascular resistance, as in conscious adults; changes in heart rate and cardiac output were variable. For the lowest block, the addition of adrenaline seemed to produce an increase in cardiac output and an increase in heart rate during the 30 min after injection.

In children, very few haemodynamic studies are available. Caudal blockade is associated with minimal haemodynamic changes (Fortuna, 1967; Melman, Pennelas and Maruffo, 1975), and no significant haemodynamic changes were reported after extradural blockade in children younger than 2 yr (Delleur et al., 1985). In the present study, pre-induction values of heart rate differed according to age. The decrease in resting heart rate in the post-natal period seems to be related to changes in intrinsic cardiac properties after birth rather than to changes in the parasympathetic or sympathetic tone (Woods et al., 1977).

Changes in arterial pressure were different in the three groups of children. In the youngest children, younger than 8 yr, extradural anaesthesia was associated with no significant changes in SAP. On the other hand, in children older than 8 yr, extradural anaesthesia was marked by a consistent decrease in SAP which was maximal 25 min after the injection of the local anaesthetic. The effect of extradural anaesthesia on SAP is, for the most part, a result of the decrease in total systemic vascular resistance in the blocked area. The lesser decrease in SAP observed in the youngest children is difficult to explain. Even in children after the first months of life, the neuro–hormonal control of resting AP and the systemic AP response to autonomic agonists are identical to those of the adult (Woods et al., 1977; Klopfenstein and Rudolph, 1978; Thornburg and Morton, 1983; Doolan and Brown, 1984). There are two other possible explanations. First, the relative blood volume of the legs in a child is smaller. Second, there is possibly a lower level of systemic vascular resistance in a child at rest.

Changes in heart rate were also different in each age group. In children younger than 2 yr a small but significant reduction in HR was observed more than 30 min after injection. In children aged between 2 and 8 yr there was no significant change. In children older than 8 yr, the HR decreased significantly, and the most important decrease was observed more than 30 min after injection. The addition of adrenaline in our study seemed to provide the same results as reported by Scott and colleagues (1977) and Murphy and associates (1976).

The decrease in HR after 30 min following extradural anaesthesia, is probably associated with a moderate decrease in cardiac output in children older than 8 yr. In children aged less than 2 yr, the reduction in HR was not always associated with a reduction in arterial pressure and, if it occurred, the decrease in arterial pressure was small.

Thus this study confirms that the use of extradural anaesthesia (combined with general anaesthesia) is marked by minimal haemodynamic changes in children younger than 8 yr. In older children, the results were similar to those previously reported in adults. Atropine seems to counteract the haemodynamic changes in adults, and could be given to children older than 8 yr before extradural anaesthesia. From a practical point of view, no "preloading" fluids were needed before performing the extradural blockade in children.

No significant difference was observed between thoracic and lumbar extradural anaesthesia in the present study, except in SAP (significant change 15 min after skin incision). The level of analgesia in the thoracic group was lower than T4 and, therefore, there was no blockade of the cardiac sympathetic nerves. The difference in SAP observed was probably the result of there being a larger vasodilated area with a decrease in the vasoconstricted, unblocked area. A similar absence of haemodynamic changes was reported by Arthur (1980). Following repair of coarctation of the aorta, this author could not obtain a reduction in arterial pressure following thoracic extradural anaesthesia using intermittent injections of bupivacaine (level of puncture T6–7).

Postoperative analgesia

One of the major advantages of using the continuous extradural technique is to allow effective postoperative pain relief, without risk of respiratory depression. Disadvantages are the necessity of either repeated injections or continuous infusion, possible motor blockade in spite of using low concentrations of solution, and possible tachyphylaxis.

Intermittent top-up injections are not recommended in adult patients because of possible tachyphylaxis and its combined risk of systemic toxicity, the risk of hypotension following reinjection, and the potential danger of break-through pain. These disadvantages are not commonly observed in children. In our experience, we never observed tachyphylaxis or hypotension. Continuous infusion should be administered with a syringe pump or a powered i.v. infusion pump because of the high resistance of the small paediatric extradural catheter. Furthermore, variations in the amount of the analgesia required in the early postoperative period are wide, even after major surgical procedures, and many children did not require any additional injection of local anaesthetics in the first 24 h after operation. However, before beginning to use extradural anaesthesia, the authors had used analgesics sparingly in the postoperative period; in children younger than 8 yr, opioids were never prescribed. Before this technique was used, postoperative pain was often underestimated and neglected, as a result of the lack of interest of both doctors and nurses. The medical staff is now more sensitive to the patients' comfort and will provide them with analgesics or extradural injections when requested. However, in the youngest children, pain is very difficult to evaluate (Mather and Mackie, 1983; Abu Saad, 1984; Owens, 1984) and top-ups are performed according to requests of parents or nurses.

No complications from the maintenance of catheters or the repeated injections were observed, but the catheters were removed from most patients on the 2nd day after operation. Recommendations are now noted on the postoperative chart that the catheter be removed on the 3rd day after operation unless the pain remains acute or if painful procedures are likely to be necessary.

CONCLUSION

Continuous extradural anaesthesia is a valuable technique in children in order to produce analgesia for surgical procedures of long duration. Avoiding the use of opioids, it allows a rapid recovery and facilitates postoperative care. Haemodynamic changes are less important in infants and young children than in older children and adults.

One should keep in mind that this technique requires trained medical staff as well as special equipment to ensure safety. Furthermore, its long term consequences have yet to be assessed.

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DOES INJECTION OF NON-DEPOLARIZING NEUROMUSCULAR BLOCKERS BEFORE THIOPENTONE AFFECT THEIR SPEED OF ONSET?

A Study of Tubocurarine and Vecuronium

I. D. LEVACK AND A. A. SPENCE

SUMMARY

In an open sequential pharmacodynamic study in 40 patients, the rate of onset of neuromuscular blockade using tubocurarine or vecuronium was measured. Comparison was made between groups of 10 patients who received thiopentone followed by either blocker and a "reverse" sequence where the blocker was injected before thiopentone. There was a small difference between groups, amounting to a few seconds in rate of onset of block, but this was not suggestive of a systematic effect of the drug sequence.

Gray and Halton (1946) in their original description of the use of tubocurarine in anaesthesia used a mixture of tubocurarine 15 mg and sodium thiopentone 500 mg as a single injection. However, Bourne (1947) recommended that tubocurarine should be injected after thiopentone from a separate syringe, because of chemical incompatability between the two solutions, and that a different vein be used. When it became evident that the onset time of tubocurarine was a few minutes, a "reversed" sequence of tubocurarine 30 mg followed immediately by injection of up to 500 mg of sodium thiopentone using the same needle became established practice for some anaesthetists, according to Lee and Atkinson (1973). It is not known whether the order of administration affects the pharmacodynamic profile of the neuromuscular blocker.

The aim of this study was to compare the onset times of neuromuscular blockade by drugs given either before or after the induction of anaesthesia with thiopentone. Tubocurarine was studied because it was the drug for which the reversed sequence was originally described, although no measurements can be found in the literature. We also studied vecuronium as an example of a drug with a relatively faster onset of action.

PATIENTS AND METHODS

Forty healthy adult patients, younger than 60 years of age, undergoing general surgery and premedicated with papaveretum 10 mg and hyoscine 0.2 mg were studied. None had any condition in which neuromuscular blockers are contraindicated. Informed verbal consent was obtained from each patient and the study was approved by the local ethics committee.

Before the induction of anaesthesia, the patient's left arm was abducted and the thumb connected to a force displacement transducer (Myograph 2000) in order to measure isometric twitch tension. A Myotest nerve stimulator delivered 0.2-ms impulses in a train-of-four (TOF) pattern (Roberts and Wilson, 1968) at 2 Hz repeated at 10-s intervals (Ali, Utting and Gray, 1970) and, after setting a pre-load of 30 g, a control recording was made in the conscious patient before the induction of anaesthesia. Discomfort arising from the nerve stimulation was minimized by giving the patient 50% nitrous oxide in oxygen delivered from a Magill breathing system. Arterial pressure in the arm was recorded and a venous cannula was inserted to a vein in the right forearm.

Drug doses were sodium thiopentone 4 mg kg^{-1},

I. D. LEVACK,* M.D., F.F.A.R.C.S.; A. A. SPENCE, M.D., F.F.A.R.C.S., F.R.C.P.GLAS.; Department of Anaesthetics, Royal Infirmary, Edinburgh EH3 9YW. Accepted for Publication: June 3, 1987.

*Present address, for correspondence: Department of Anaesthetics, Foresterhill, Aberdeen Royal Infirmary, Aberdeen AB9 2ZB.

TABLE I. *Duration and sequence of drug administration (10 patients in each group)*

← 5 s →	30-s pause	← 5 s →
Group 1: Thiopentone 4 mg kg^{-1}		Vecuronium 0.1 mg kg^{-1}
Group 2: Vecuronium 0.1 mg kg^{-1}		Thiopentone 4 mg kg^{-1}
Group 3: Thiopentone 4 mg kg^{-1}		Tubocurarine 0.5 mg kg^{-1}
Group 4: Tubocurarine 0.5 mg kg^{-1}		Thiopentone 4 mg kg^{-1}

vecuronium 0.1 mg kg^{-1} and tubocurarine 0.5 mg kg^{-1}; the sequences and speeds of injection are shown in table I. Each injection was given over a period of 5 s, with an intervening period of 30 s. Ventilation of the lungs was assisted as appropriate by manual inflation with 70% nitrous oxide in oxygen until there was 90% depression of the control twitch height in T1. Arterial pressure was measured before tracheal intubation; the lungs were ventilated artificially with 0.5% halothane in 70% nitrous oxide and oxygen using a conventional automatic ventilator.

The onset time of blockade was measured from the time of injection of the neuromuscular blocker, regardless of the sequence with thiopentone. The indices sought were 50% and 90% depression of control T1, and T4/T1 at 30%, 50% and 70% depression of control height in T1.

All patients were visited on the day after operation and specific enquiry was made as to any discomfort during the control recording while breathing the mixture of nitrous oxide before induction of anaesthesia.

Results are presented as mean values (±SD). Where appropriate, mean values were compared using the unpaired Student's *t* test.

RESULTS

The four groups were broadly comparable with respect to age and body weight, although group 2 patients were on average older and heavier (table II).

Onset of neuromuscular blockade

The times from injection of the neuromuscular blocker to 50% and 90% depression of T1 in a TOF from control are shown in table III. In groups 1 (thiopentone–vecuronium) and 2 (vecuronium–thiopentone), 50% depression was achieved with vecuronium to within 1 s irrespective of sequence with sodium thiopentone, although the mean time to the same level of depression following tubocurarine was 9 s faster when tubocurarine was given first (group 4) ($P < 0.001$).

Time to 90% depression by tubocurarine was twice as long as that for vecuronium. There was a difference of 13 s between groups 3 and 4 ($P < 0.001$) and 6 s between groups 1 and 2 ($P < 0.001$), but these do not suggest a systematic effect of drug sequence.

Tracheal intubation was carried out with ease at 90% depression in all patients by the same anaesthetist and no detailed assessment of intubating conditions was attempted. Systolic arterial pressure measured before tracheal intubation was greater than 95 mm Hg in every patient.

On the day after operation no patient complained that nerve stimulation (supramaximal) was painful, and it was usually described as a tapping sensation. There was no report of any muscle weakness or discomfort.

Characteristics of neuromuscular blockade

The relationship between T1 depression and TOF ratio following either blocker was not affected by reversing the sequence with sodium thiopentone (table IV). It was also evident that the degree of fade for a given level of T1 depression was greater with tubocurarine than with vecuronium at the doses given.

TABLE II. *Mean values ±SD of age and body weight*

	Age (yr)	Body weight (kg)
Group 1	40±16	61.7±5.5
Group 2	47±16	68.5±9.1
Group 3	40±15	63.1±4.9
Group 4	39±11	61.2±6.2

TABLE III. *Onset times (s) of neuromuscular blockade. Mean values ±SD after vecuronium (V) (groups 1 and 2) and tubocurarine (Tc) (groups 3 and 4). T = 2.5% thiopentone*

Depression of T1	Group 1 (T–V)	Group 2 (V–T)	Group 3 (T–Tc)	Group 4 (Tc–T)
50%	74±19	73±23	77±24	68±29
90%	109±27	103±46	210±46	223±41

TABLE IV. *Train-of-four ratios (mean ± SD) during onset of block after vecuronium (groups 1 and 2) and tubocurarine (groups 3 and 4) (mean ± SD)*

T1 *v.* control	Group 1 (T–V)	Group 2 (V–T)	Group 3 (T–Tc)	Group 4 (Tc–T)
70%	81±3	83±3	70±4	73±7
50%	72±3	75±4	58±5	62±9
30%	63±6	68±5	42±9	39±6

DISCUSSION

It is known that thiopentone has a direct stimulant action on muscle and prolongs the contraction time (Quilliam, 1955), but there is a simultaneous depression of neuromuscular transmission (Sirnes, 1954). A synergistic effect between sodium thiopentone and tubocurarine has been described by Dundee (1974), and Hughes (1970) showed that thiopentone potentiates the action of tubocurarine in cats, in particular the recovery time. On the other hand, cardiovascular depression after sodium thiopentone, with delay in circulation time, might be expected to slow the arrival of neuromuscular blockers at their site of action.

In spite of small, statistically significant, differences in some of the indices analysed for tubocurarine or for vecuronium, the results did not reveal either a systematic or a clinically significant difference in the pharmacodynamics of these drugs, in the doses given, when preceded or followed by thiopentone at the induction of anaesthesia.

Thus, intrinsically, there is neither advantage nor disadvantage in the reversed sequence regimen as seen with these compounds. Obviously, the prior injection of the neuromuscular blocker may help to ensure that its efficacy as regards conditions for tracheal intubation coincides with the peak anaesthetic effect of thiopentone. This presumed advantage, however, confers no obvious benefit in terms of induction–intubation interval as considered in relation to the unprotected airway. The patient is in an irretrievable process involving aspiration and ventilatory risk from the moment of the first injection, whether it be neuromuscular blocker or hypnotic.

The original intention with the reversed sequence (tubocurarine–thiopentone) was to shorten the interval between the start of induction of anaesthesia and the onset of suitable conditions for tracheal intubation. This aspect was not examined directly in the present study. Indeed, we waited deliberately until we saw 90% depression of T1 because we believed that this would yield good conditions for intubation, as was the case.

The difference in TOF ratio and T1 depression (table IV) following vecuronium or tubocurarine is probably attributable to the different pharmacodynamics and sites of action of the two drugs at the neuromuscular junction (Bowman, 1980).

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USE OF NEOSTIGMINE IN THE ANTAGONISM OF RESIDUAL NEUROMUSCULAR BLOCKADE PRODUCED BY VECURONIUM

J. E. JONES, J. M. HUNTER AND J. E. UTTING

SUMMARY

Recovery from neuromuscular block produced by vecuronium was studied in 50 patients using electromyography and the train-of-four technique. Twenty patients received neostigmine 2.5 mg, 10 when the initial response of the train-of-four was 50% of control and 10 when it was 10%. Neostigmine 5 mg was investigated in a similar manner and in 10 patients spontaneous recovery was studied. In all patients the time to 70% recovery of the initial response and of the train-of-four ratio was followed. Neostigmine significantly reduced the time to 70% recovery of both ratios with both degrees of block, but neostigmine 5.0 mg did not give a substantially more rapid recovery than 2.5 mg. No evidence of a neostigmine-induced block was encountered. Neostigmine 2.5 mg was rapidly effective in antagonizing vecuronium-induced block, even when initial recovery was only slight: there was no advantage in using neostigmine 5.0 mg.

Vecuronium has a shorter duration of action than pancuronium and recovery from neuromuscular blockade is more rapid with the newer drug (Crul and Booij, 1980). It has been suggested that, when given in bolus doses, an anticholinesterase may not be necessary to antagonize vecuronium-induced neuromuscular block (Baird, Bowman and Kerr, 1982), although when the agent is given by infusion, neostigmine is required in a dose similar to that needed after an infusion of pancuronium (Gencarelli and Miller, 1982).

Using the train-of-four (TOF) method of stimulation, and recording electromyographically, antagonism of neuromuscular block after bolus doses of vecuronium has been studied, using both a larger (5.0-mg) and a smaller (2.5-mg) dose of neostigmine. The basic plan of the study was similar to that of Fox, Keens and Utting (1987).

A study using tetanic rates of stimulation has suggested that a large dose of neostigmine may itself cause neuromuscular blockade (Payne, Hughes and Al Azawi, 1980). Signs of increased blockade using the TOF were, therefore, sought, —especially when the larger doses of neostigmine were given to those with the least degree of block.

PATIENTS AND METHODS

Following approval by the hospital ethics committee, informed consent was obtained from 50 patients undergoing general or gynaecological surgery. All patients were graded as ASA I or II and were free from any neurological disorder. Patients were randomly allocated to one of five groups. In the first group of 10 patients, spontaneous recovery after vecuronium was followed; in a second group of 10, neostigmine 2.5 mg was given to antagonize neuromuscular block when the ratio of the first response to the train-of-four to control (A′/A) was 10% and in the third group of 10, neostigmine 2.5 mg was given when A′/A had reached 50%; similarly, in the fourth group of 10 patients neostigmine 5.0 mg (in two 2.5-mg doses given 2 min apart) was given to patients when recovery was 10% and in the fifth group of 10 it was given when recovery was 50%. On every occasion the first dose of neostigmine was preceded by atropine 1.2 mg. A further dose of atropine 0.6 mg preceded a second dose of neostigmine.

J. E. JONES, M.B., F.F.A.R.C.S.; J. M. HUNTER, M.B., F.F.A.R.C.S.; J. E. UTTING, M.B., F.F.A.R.C.S.; University Department of Anaesthesia, Royal Liverpool Hospital, Prescot Street, P.O. Box 147, Liverpool L69 3BX. Accepted for Publication: March 11, 1987.

Premedication was with promethazine 50 mg orally the night before operation, with or without diazepam 10 mg orally 3 h before the procedure, or with a combination of morphine 10 mg and cyclizine 50 mg (Cyclimorph) i.m. 1 h before the operation. The different types of premedication were randomly distributed between the five groups. Anaesthesia was induced with thiopentone, fentanyl and either droperidol or a small dose of midazolam, according to the preference of the anaesthetist. Each patient then breathed 70% nitrous oxide and oxygen using a Magill breathing system without the addition of a volatile agent. Ventilation was assisted as necessary to maintain the end-tidal carbon dioxide tension between 4.75 and 5.25 kPa (Normocap; Datex).

A control trace of the EMG was obtained. ECG electrodes (Deva Medical) were placed over the ulnar nerve at the wrist to act as stimulating electrodes and recording electrodes were placed over the adductor pollicis brevis and the base of the index finger on the palm of the hand. A copper earth electrode was strapped on the wrist between the recording and stimulating electrodes. Single pulse stimuli of increasing voltage were delivered to the ulnar nerve until the maximum height of the compound muscle action potential (CMAP) was achieved. The voltage was then increased a further 25% to ensure supramaximal stimulation. Stimulation then proceeded with train-of-four supramaximal stimuli (0.2 ms; 2 Hz) at 12-s intervals and the resulting control train-of-four CMAP recorded (at least 10 responses being obtained). The height of the peak deflection of the CMAP was measured. After the control readings had been completed, vecuronium 100 $\mu g\, kg^{-1}$ was injected and intubation of the trachea carried out when clinically appropriate.

Recovery was monitored using both the ratio of the first twitch of the train to control (A′/A) and the ratio of the fourth twitch to the first (D′/A′, the train-of-four ratio). The train was repeated at 1-min intervals until the administration of neostigmine was imminent, when the intervals were reduced to 12 s until the end of the study. In those patients allowed to recover spontaneously, the TOF was repeated at 12-s intervals from recovery of 10% A′/A until the end of the study. Increments of vecuronium 40 $\mu g\, kg^{-1}$ (up to a maximum of four) were given when the ratio A′/A had returned to 10%. However, no increments were given to those in whom recovery was spontaneous.

The times measured were the times until A′/A and D′/A′ had attained 70% (the latter taking longer). As A′/A was always found to return to within 10% control, it was not deemed necessary to adjust for zero drift of the EMG. Zero times for the group which recovered spontaneously were taken as being when the A′/A were exactly 10% and 50%. When neostigmine 2.5 mg was given at either of the two degrees of block, zero time was taken when it was actually administered; when two doses of neostigmine were given, zero time was taken at the administration of the first dose.

In the group in which recovery was spontaneous, monitoring was continued until D′/A′ had reached 70%. In patients who received neostigmine, monitoring was continued for at least 10 min after the agent had been given in the case of patients with a block of 50% and, in those with 90% block, at least 20 min or until 70% recovery of the TOF ratio (D′/A′) had been achieved and maintained for 10 min. When the study had been completed and neuromuscular monitoring discontinued, the patient was allowed to breathe 100% oxygen spontaneously through the tracheal tube until the airway was considered safe. The trachea was then extubated.

Statistical analysis of the differences between the means was carried out using Tukey's method.

RESULTS

Details of the age, weight and sex of the patients studied are given in table I. Table II shows the mean times to 70% recovery of both A′/A and D′/A′ for spontaneous recovery and for the two different doses of neostigmine. Statistical analysis shows that recovery in terms of both A′/A and D′/A′ was significantly accelerated in each instance by the administration of neostigmine ($P < 0.01$). However, the analysis also shows that in each case the difference in recovery time between administering two doses of neostigmine rather than one dose was not significant.

Thus, the time for spontaneous recovery to A′/A 70% from the greater degree of block (A′/A 10%) was 15.5 min, the train-of-four ratio (D′/A′) taking 24.2 min to reach 70%. This compares with 3.9 min (A′/A) and 9.2 min (D′/A′) following a single bolus of neostigmine 2.5 mg. Increasing the dose of neostigmine from 2.5 mg to 5 mg produced very similar recovery times of 3.4 min for A′/A and 5.6 min for D′/A′.

TABLE I. *Mean age and weight (SD) of the groups of patients studied and the male/female (M/F) ratio (n = 10 in each group). The initial block was measured by the ratio A'/A. The dose of neostigmine is indicated; in the group given 5.0 mg the dose was divided; in the spontaneous group no neostigmine was given*

	Initial block	Age (yr)	Weight (kg)	M/F
Spontaneous	10+50%	41.3 (14.7)	72.2 (11.3)	6/4
Neostigmine 2.5 mg	10%	44.2 (22.7)	64.4 (12.9)	5/5
	50%	45.1 (14.1)	70.1 (11.4)	4/6
Neostigmine 5.0 mg	10%	34.4 (8.8)	74.2 (14.8)	5/5
	50%	43.5 (18.8)	62.1 (14.9)	5/5

TABLE II. *Recovery time (min (SD)) to 70% of ratios A'/A and D'/A' for the two degrees of block studied (i.e. when A'/A initially was 50% and 10%). Spontaneous recovery is compared with the use of neostigmine in one and two doses* n = *10 in each group. Neostigmine in both doses significantly accelerated the rate of recovery of both variables when compared with spontaneous recovery.* (P < *0.01 in each case; Tukey's method). The difference in recovery rates between the two doses is not statistically significant*

Initial block A'/A	Ratio	Time to 70 % recovery of ratio (min)		
		Spontaneous	Neostigmine 2.5 mg	Neostigmine 2.5+2.5 mg
50 %	A'/A	4.9	1.2	1.1
		(2.7)	(0.68)	(0.74)
	D'/A'	6.9	2.1	1.5
		(3.2)	(1.0)	(0.53)
10 %	A'/A	15.5	3.9	3.4
		(6.8)	(2.24)	(1.3)
	D'/A'	24.2	9.2	5.6
		(11.4)	(5.3)	(3.7)

The time for spontaneous recovery of A'/A to 70% from a lesser degree of block (A'/A 50%) was 4.9 min and of the train-of-four ratio (D'/A') was 6.9 min. Following a single dose of neostigmine 2.5 mg at 50% A'/A, the duration of recovery of A'/A was significantly reduced, to 1.2 min. The recovery time of the train-of-four ratio to 70% (D'/A') was also significantly reduced, to 2.1 min. Administration of neostigmine 5 mg in this group produced recovery times of 1.1 min for A'/A and 1.5 min for D'/A'.

Not evident from table II is the fact that, in the group in which recovery was spontaneous (and to whom no increments were given), the times from the administration of vecuronium 100 mg kg^{-1} to 70% recovery were A'/A 39.6 (12.2) min, and of D'/A' 54.4 (18.9) min (table III).

TABLE III. *Mean times (min (SD)) to 70% spontaneous recovery of A'/A and D'/A' following single dose vecuronium or atracurium. Data for atracurium from Fox, Keens and Utting (1987)*

	A'/A	D'/A'
Vecuronium (*n* = 10)	39.6 (12.2)	54.4 (18.9)
Atracurium (*n* = 4)	57.5 (11.4)	65.5 (11.8)

In addition, it was found that the administration of neostigmine, even when 5.0 mg was administered to those with the lesser degree of block, was always followed by an acceleration of recovery of both of the ratios studied. In every patient studied, both A'/A and D'/A' ratios continued to increase. Thus no evidence of fade was seen which could have been interpreted as evidence of neostigmine-induced blockade.

DISCUSSION

This study demonstrates the marked acceleration of recovery which may be achieved by the administration of neostigmine 2.5 mg. This acceleration was greatest when antagonism was undertaken at the greater degree of block (A'/A = 10%) when the time to 70% recovery of the train-of-four ratio was reduced from a mean of 24 min for spontaneous recovery to 9 min following neostigmine 2.5 mg, a train-of-four ratio of 70% being considered to be the point at which recovery from block was adequate and safe (Brand et al., 1977). Although a larger dose of neostigmine administered to patients with this degree of block produced an even faster rate of recovery, the difference for D'/A' was only of the order of

3.5 min and was of neither statistical nor clinical significance.

The acceleration of recovery was considerably less when neostigmine was given when there was already 50 % recovery A′/A. At this time, neostigmine 2.5 mg reduced the recovery time of D′/A′ from a mean of 7 min for spontaneous recovery to 2 min following the neostigmine. A second dose of neostigmine tended further to shorten recovery time, but again this was unimportant.

Every patient made a rapid and complete recovery. Payne, Hughes and Al Azawi (1980) showed, with tubocurarine, dimethyl tubocurarine and gallamine, that an increase in tetanic fade (at 50 Hz) could follow a second dose of neostigmine 2.5 mg,—an effect which was most marked during the administration of 2 % halothane. No parallel effect was demonstrated here but, of course, had halothane been used as an adjuvant to anaesthesia or tetanic stimulation used as the method of assessing neuromuscular blockade, or both, fade might have been demonstrated.

It appears from this study that a full clinical recovery from vecuronium-induced neuromuscular blockade can be achieved at a mean time of about 10 min after the administration of neostigmine, even when the degree of recovery at which neostigmine is injected is small and the dose of neostigmine only 2.5 mg. However, as with other non-depolarizing neuromuscular blocking agents, there is considerable individual patient variation in the rates of recovery. For example, in one patient in the study it took 19 min for recovery of D′/A′ to 70 % following neostigmine 2.5 mg injected when A′/A was 10 %, compared with a mean time of 9 min. Similarly, a considerable scatter in the rates of spontaneous recovery was seen, one patient taking 84 min from the time of administration of the initial bolus dose of vecuronium to show recovery of the train-of-four ratio to 70 %. This is some 30 min longer than the mean time of 54 min in the 10 patients studied. The scatter is similar to that reported by Fox, Keens and Utting (1987) for spontaneous recovery of atracurium-induced neuromuscular blockade.

Driessen and co-workers (1985) have described dose-dependent potentiation of vecuronium by midazolam in the rat. Using very large doses (0.5 and 5 mg kg^{-1}), depression of twitch height by 17 % and 34 %, respectively, was observed once a steady state blockade of the twitch height had been induced by vecuronium. In our study, only six patients received midazolam and these were randomly distributed between the groups. The mean dose of midazolam was 0.06 mg kg^{-1}, the maximum in one patient being 0.1 mg kg^{-1}. Presupposing a response in man similar to that in the rat, any potentiation of block is likely to be small, and in any event, is unlikely greatly to influence measured time between specific percentage recoveries from neuromuscular blockade.

In ideal circumstances, during clinical anaesthesia neuromuscular function would be measured and recorded using either mechanical (strain gauge) or electromyographic techniques, but this is not usually possible. Merely using tactile or visual assessment of the train-of-four ratio is unreliable during recovery, when the degree of block depends on assessing fade (Viby-Mogensen et al., 1985). In the absence of sophisticated monitoring of neuromuscular function, it is advisable always to antagonize the action of vecuronium unless anticholinesterases are contra-indicated or the degree of recovery is almost complete. This is especially so since individual rates of recovery vary greatly. Neostigmine 2.5 mg produces rapid recovery from neuromuscular blockade produced by vecuronium; neostigmine 5.0 mg is unnecessary, at least if some degree of recovery is already apparent.

The current study was conducted using a design almost identical to that used by Fox, Keens and Utting (1987) in a study of atracurium; a comparison of the results obtained is, therefore, of some value. Once A′/A had reached 10 %, recovery from vecuronium was considerably faster than from atracurium, whether or not neostigmine was given. However, taking the time from an initial dose to 70 % spontaneous recovery of the train-of-four ratio (when the patient can be considered clinically to be "safe") gives another interesting comparison (table III). The times are 66 (12) min for atracurium and 54 (18.9) min for vecuronium. Unless the action of the drugs is terminated by neostigmine, neither can be considered to be short-acting and the difference between them in terms of duration of action is quite small. Once the first response to the train-of-four has re-appeared, however, recovery from vecuronium is more rapid than with atracurium, and when all four responses have returned it is very much faster.

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EFFECTS OF TEMPERATURE ON THE INTERACTION OF MORPHINE WITH OPIOID RECEPTORS

M. M. PUIG, W. WARNER, C. K. TANG, M. L. LAORDEN AND H. TURNDORF

SUMMARY

The electrically stimulated guineapig ileum preparation was used to determine the effects of temperature on the affinity of morphine for opioid receptors. The potency of morphine (expressed as the concentration which produces 50% inhibition—IC_{50}) was significantly decreased at 30 °C (IC_{50} 41.0 × 10^{-8} mol litre^{-1}) and increased at 40 °C (IC_{50} 5.1 × 10^{-8} mol litre^{-1}) when compared with its potency at 37 °C (IC_{50} 8.8 × 10^{-8} mol litre^{-1}). Experiments carried out in the presence of naloxone (a competitive opioid antagonist) indicated that the affinity of opioid receptors for this antagonist was not affected by temperature. Further studies using B-funaltrexamine (a mu-specific, non-reversible opioid antagonist) revealed an increase in morphine receptor affinity when temperature was increased from 30 to 37 °C. The data demonstrated that the potency of morphine increased with temperature; the affinity of naloxone for opioid receptors was unaltered by temperature; and the affinity of morphine for mu-receptors reached an optimal value within the range 30–37 °C.

The consequences of changes in temperature on the activity and dose requirements of opioids are poorly defined. However, it is known that both hypo- and hyperthermia can affect drug requirement during anaesthesia. For example, the MAC of volatile anaesthetics (as a measure of anaesthetic requirement) increases during hyperthermia (Steffey and Eger, 1974) and decreases with hypothermia (Vitez, White and Eger, 1974). Similarly, non-depolarizing neuromuscular blocking drugs are affected by body temperature: less pancuronium or tubocurarine is required during hypothermia in most clinical situations (Miller et al., 1978). In the present study we have considered whether changes in temperature would affect the interaction of morphine with its specific receptors in the electrically stimulated myenteric plexus-longitudinal muscle guineapig ileum (MPLM). In this preparation the binding of opioids to their receptors leads to a decrease in the ganglionic release of acetylcholine (Paton and Zar, 1968). This in turn produces an inhibition of the electrically-induced smooth muscle contractions. The MPLM has been used widely to demonstrate pharmacological effects of opioids because: (1) very small concentrations are sufficient to produce an effect; (2) the effects are reversed by naloxone; (3) there is a close correlation between opioid analgesic potency in man and potency in inhibition of ileal activity; and (4) it contains a high concentration of mu-opioid receptors (Kosterlitz and Waterfield, 1975). This point is especially relevant, since most opioids used in anaesthesia are strong mu-agonists (Vaught, Rothman and Westfall, 1982). Finally, use of this preparation obviates most pharmacokinetic variables, thus simplifying the interpretation of results.

MATERIALS AND METHODS

All investigations were carried out on the guineapig ileum MPLM preparation. Male albino

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Margarita M. Puig, m.d., ph.d., Chau-Kvei Tang, m.d.; Herman Turndorf; Department of Anesthesiology, NYU Medical Center, 550 First Avenue, New York, NY 10016, U.S.A. William Warner, ph.d., Department of Pharmacology, NYU College of Dentistry, New York. Maria Luisa Laorden, m.d., Department of Pharmacology, Murcia University School of Medicine, Murcia, Spain. Accepted for Publication. April 6, 1987

Correspondence to M.M.P.

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guineapigs (English Short Hair) weighing 300–400 g were stunned by a blow to the head and immediately decapitated. The abdomen was opened and the MPLM prepared as described previously (Puig, Gascon and Musacchio, 1978). Each strip of tissue, weighing 25–30 g, was suspended in a 10-ml organ bath containing Krebs-bicarbonate solution equilibrated with 95 % oxygen plus 5 % carbon dioxide. The strips were placed under a resting tension of 0.3 g and were allowed to equilibrate for 60 min before the start of the definitive investigations. The MPLM preparation was stimulated with platinum ring electrodes placed at the top and bottom of the muscle strip and separated by a distance of 6.0 cm. Symmetrical, biphasic stimuli of 1 ms duration and supramaximal voltage (35 V) were generated by a Grass S-88 stimulator, mixed with the aid of two Grass stimulus isolation units (SIU 5), fed into a Crown DC 300 audio amplifier and then applied to the electrodes. The voltage and duration of the stimuli were monitored constantly on a Tektronix R5103N oscilloscope. Strips were stimulated at a frequency of 0.1 Hz throughout all studies. Isometric contractions of the muscle were registered by means of a Grass force transducer (model FTO3C) coupled to a Grass polygraph recorder. Bath temperature was maintained at 30, 37 or 40 °C. Morphine solutions (morphine sulphate) were made daily in glass-distilled water and added to the organ bath in volumes of up to 0.2 ml. The drug was kept in the bath for a period of 5 min while the effect of the agonist was measured, after which the preparation was washed with drug free Krebs-bicarbonate solution. In some investigations, naloxone (naloxone hydrochloride 1×10^{-9} to 3×10^{-8} mol litre^{-1}) or B-funaltrexamine (beta-funaltrexamine hydrochloride 7.5×10^{-9} mol litre^{-1}) was added directly to the bath during the initial equilibration period and remained present throughout the entire experiment.

When the maximal effect of each dose of morphine was attained, the height of the contractions was compared with pretreatment values. Percent inhibition was then plotted against the log dose of morphine. This procedure was repeated for each temperature and dose of naloxone. The slopes of the individual curves and their 95 % confidence limits were compared as a means of testing for parallelism. Log dose–response curves were used to determine the IC_{50} of morphine (the dose of morphine which produced a 50 % inhibition of the amplitude of contraction).

The pA_2 values of naloxone were derived from Schild plots (Arunlakshana and Schild, 1959) by the method of Tallarida and Murray (1981). A competitive antagonist produces a parallel shift of the dose–response curve of an agonist. The displacement of the curve is dose-related; the higher the concentration of the antagonist the greater the shift of the curve. The pA_2 is the negative log of that antagonist concentration which produces a two-fold shift of the dose–response curve. This value is numerically equal to the log of the dissociation constant of the antagonist (Arunlakshana and Schild, 1959). Schild plots allow the calculation of pA_2 values and also verify (if the slope of the line is -1) the competitive nature of the blockade. The dissociation constant of an antagonist is equal to the reciprocal of its affinity for the receptor under investigation.

The dissociation constant of morphine for its receptors was determined by the method of Furchgott and Bursztyn (1967). Using this procedure, dose–response curves for morphine were obtained before and after exposure to the irreversible antagonist B-funaltrexamine (Ward, Portoghese and Takemori, 1982). Equiactive doses of morphine were plotted in a double reciprocal manner and the dissociation constant (K_A) of the agonist were determined. IC_{50} (a measure of potency of the agonist), K_A (a measure of affinity of the agonist) and pA_2 (a measure of affinity of the antagonist) were determined at 30, 37 and 40 °C. Statistical analyses were performed by the Dunnett's test (comparision of several treatment groups with a control) and Students's t test (Tallarida and Murray, 1981).

RESULTS

Effects of temperature on the dose–response relationship of morphine in the MPLM preparation

Log dose–response curves for morphine were constructed with data obtained from experiments carried out at 30, 37 and 40 °C. From these curves, the IC_{50} was calculated. At 37 °C, 50 % inhibition of the electrically induced muscle contraction occurred at a morphine concentration of 8.8×10^{-8} mol litre^{-1}. Studies performed at 30 °C and 40 °C demonstrated a statistically significant change in the potency of the agonist ($P < 0.05$) (table I). At 30 °C, morphine was one-fifth as potent, and at 40 °C was almost twice as potent, as in control experiments carried out at 37 °C. A

TABLE I. *Effects of temperature (95% confidence limits) on dose–response curves of morphine. All IC_{50} values are significantly different from each other ($P < 0.05$). Each IC_{50} represents the results from 10 experiments*

	Temperature (°C)		
	30	37	40
IC_{50} ($\times 10^{-8}$ mol litre^{-1})	41 (30–57)	8.8 (6–13)	5.1 (4.4–5.8)
Relative potency	0.21	1.0	1.7
Slope of curve	38 (28–48)	48 (32–65)	46 (31–60)

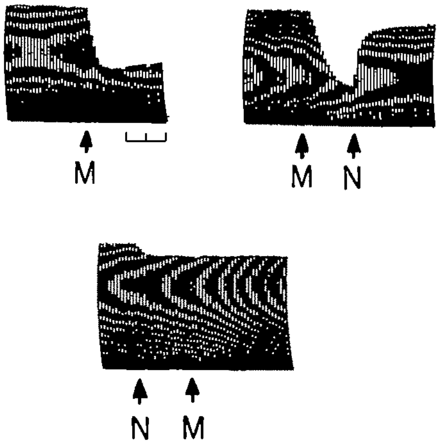

FIG. 1. Effect of morphine 2×10^{-7} mol litre^{-1} (M) and naloxone 10^{-7} mol litre^{-1} (N) on the electrically induced contractions of the MPLM at 37 °C. Drugs were added to the organ bath in 0.1-ml volumes. Time marker = 1-min intervals.

comparison of the slopes showed that they did not differ significantly, indicating that all log dose–response curves were parallel. Thus, changes in temperature altered equally the response to all doses of morphine tested.

Effects of naloxone on the response to morphine at different temperatures

Naloxone, a pure opioid antagonist, blocked the response to morphine in the MPLM ileum preparation (fig. 1). A series of experiments was performed to determine log dose–response curves of morphine in the presence of various concentrations of naloxone (within the range 1×10^{-9} to 3×10^{-8} mol litre^{-1}) at 30, 37 and 40 °C. With increasing concentration of antagonist, dose–response curves shifted to the right, causing a decrease in the potency of the agonist (table II). For each temperature examined, naloxone produced a parallel shift in the morphine dose–response curves. Thus, for each concentration of naloxone the potency of morphine increased as the temperature was increased. These data confirm that the competitive nature of the morphine–naloxone interaction was not significantly changed by temperature.

To determine whether changes in temperature modified the binding characteristics of opioid receptors, we constructed Schild plots from the data. The resulting pA_2 values measured the dissociation constant of a competitive antagonist for the receptors, and have been widely used to distinguish between different types of opioid

TABLE II. *Effects of naloxone on the potency of morphine. 95% Confidence limits in parentheses.* * *Significantly different from response at 37 °C ($P < 0.05$)*

Naloxone concentration (mol litre^{-1})	IC_{50} of morphine ($\times 10^{-6}$ mol litre^{-1})		
	30 °C	37 °C	40 °C
1×10^{-9}	1.40 (1 0–1.9)*	0.26 (0.22–0.33)	–
3×10^{-9}	4.90 (4.2–5.7)*	1.00 (0.75–1.4)	0.61 (0.34–1.1)
30×10^{-9}	13.00 (12–14)*	5.10 (4.5–5.8)	2.70 (2.0–3.6)*

TABLE III. *Effects of temperature on pA_2 of naloxone and dissociation constant (K_A) of morphine. K_A, pA_2 and slopes expressed as mean ± SEM.* n = *number of experiments. Slope is that of the Schild plot. These values do not differ significantly from each other*

	Temperature (°C)		
	30	37	40
pA_2	9.36 ± 0.13	9.36 ± 0.19	9.67 ± 0.30
n	15	23	15
Slope	-1.1 ± 0.10	-0.9 ± 0.10	-0.8 ± 0.10
K_A ($\times 10^{-7}$ mol litre^{-1})	45.5 ± 15	8.3 ± 2.45	$7.90 \pm 0\ 56$
n	3	3	3

receptor. As shown in table III, the curves obtained at each temperature had slopes which did not differ significantly from −1. This further confirms the competitive nature of the blockade and validates the use of this method of analysis. Since pA_2 values did not change with increasing temperature we can conclude that the dissociation constant of naloxone for the receptors was unchanged in these experimental conditions.

Effects of temperature on the affinity of morphine for opioid receptors

A series of investigations was undertaken in which mu-opioid receptors were inactivated by addition of B-funaltrexamine 7.5×10^{-9} mol litre^{-1} to the preparation. The affinity of morphine for its receptors was determined from dose–response curves obtained under these and control conditions. The above procedures were carried out at 30, 37 and 40 °C. Table III shows that the dissociation constant (reciprocal of affinity) decreased as the temperature was increased from 30 to 37 °C. However, there was no change in this value when the temperature was further increased to 40 °C.

DISCUSSION

This study demonstrated that the effect of morphine on the electrically-induced contractions of the myenteric plexus–longitudinal muscle preparation was temperature dependent. The potency of the alkaloid increased directly and significantly with increases in the temperature of the organ bath. As the temperature was increased from 30 to 37 °C, the potency increased five-fold, and when the temperature was increased to 40 °C the potency was further increased by almost another two-fold. This range of temperatures was chosen because it included the range of temperature experienced by patients during surgery or in the immediate postoperative period. The parallelism of the log dose–response curves demonstrated that the effect of temperature was similar at all degrees of tissue response.

The temperature-dependent change in the activity of morphine could have been caused by any of a number of events at the effector site. Pharmacokinetic changes can be ruled out since this *in vitro* preparation does not metabolize or redistribute opioids. However, variations in temperature could have altered the number of binding characteristics of mu receptors (the predominant receptor type in the MPLM), or could have unmasked different opioid receptor subtypes.

These studies did not permit an estimation of the actual number of available receptors; however, it was possible to determine the identity and binding characteristics of the predominant receptor type by the use of Schild plots (Tallarida and Murray, 1981). From this procedure, which has been extensively used to characterize opioid receptors, the pA_2 was derived. This value is an estimation of the dissociation constant of a competitive antagonist, in this case naloxone, for its receptor. The pA_2 obtained in the present study was similar to that found by other investigators (Kosterlitz and Watt, 1968) for mu receptors, and did not change within the temperature range studied. This demonstrated that the mu receptor remained the principal receptor type within the 30–40 °C temperature range, and that the binding characteristics of naloxone with these receptors in the ileal muscle did not undergo significant change.

The change in potency of morphine that was observed at different temperatures could be related to a change in the dissociation constant of the opioid for the mu receptor. The dissociation constant (the reciprocal of affinity) of morphine decreased approximately six-fold as the temperature was increased to 37 °C. This represented an increase in affinity as the temperature approached physiological values. However, no significant change in the dissociation constant was observed as the temperature was further increased to 40 °C. This finding may be explained as: (1) the dissociation constant of morphine for its receptors reached an optimal value within the 30–37 °C range or (2) the increase in temperature (from 37 to 40 °C) might not have been sufficient to reveal a significant change in this constant.

On the basis of these observations, we suggest that the decrease in the potency of morphine during hypothermia can be explained by a decrease in its affinity for the mu receptor. Furthermore, these results indicate that the binding of naloxone to the mu receptor was not affected by changes in temperature (as indicated by the pA_2 values). This suggests that temperature differentially affects the action of agonists and antagonists as previously demonstrated in binding studies using brain membranes (Simantov, Snowman and Snyder, 1976).

Opioids are used commonly in anaesthetic practice in patients with hypo- and hyperthermia. Previous studies have demonstrated that changes in body temperature affect the MAC of inhalation anaesthetics as well as the duration and dose requirements of non-depolarizing myoneural blockers. However, the question of opioid requirements during hypo- and hyperthermia has not been addressed in the anaesthetic literature.

The effects of temperature on dose requirements of drugs are the result of changes in both pharmacokinetic and pharmacodynamic variables. That is, temperature may change the distribution, biotransformation or excretion of drugs, or the interaction with their ultimate sites of action. Since opioids produce all their pharmacological effects by binding to specific receptors (Simon, Hiller and Edelman, 1973), we have studied the effects of hypo- and hyperthermia on the opiate–receptor interaction in the guineapig ileum MPLM preparation. Our results demonstrated that larger doses of opioids were needed to produce a given effect during hypothermia, while lower doses were needed during hyperthermia. Furthermore, our data indicated that naloxone was equally effective in reversing the effects of opioids at different temperatures. This finding supports the clinical observations that naloxone is equally effective in reversing the respiratory depression of opioids on emergence from general anaesthesia when patients present with moderate hypothermia (34–35 °C).

Several investigators have demonstrated that the MAC of inhalation anaesthetics is reduced during hypothermia and that cold itself seems to be "anaesthetic" (Regan and Eger, 1967), suggesting an additive effect of hypothermia and general anaesthetics. These results reflect the net effects of temperature on both pharmacokinetics and pharmacodynamics of inhalation anaesthetics. Unlike the case for opioids, no specific binding sites or receptors have been described for inhalation anaesthetics; consequently, because of differences in their mechanism of action, the effects of temperature on dose requirements of both groups of drugs cannot be compared.

The effects of temperature on morphine requirements are comparable to those observed on the pharmacodynamics of non-depolarizing neuromuscular blockers. Thus, the concentration of tubocurarine needed to produce neuromuscular blockade was greater during hypothermia both *in vitro* (Holmes, Jenden and Taylor, 1951) and *in vivo* (Ham et al., 1978) than at physiological temperature. However, hypothermia also decreased serum clearance and elimination of tubocurarine and the net effect of both opposing changes was a prolongation of the neuromuscular blockade at low temperatures. In a similar manner, our results demonstrate that higher concentrations of morphine are needed at the opioid receptor during hypothermia. The correlation of our results on the effects of temperature on opioid activity, together with pharmacokinetic studies *in vivo*, may contribute to a rationale for the establishment of dose requirements of opioids and opioid antagonists at different body temperatures.

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VARIATIONS IN THE FLOW OF CEREBROSPINAL FLUID THROUGH SPINAL NEEDLES

S. P. GERRISH AND J. E. PEACOCK

SUMMARY

The dimensions of currently available spinal needles (0.7 mm (22-gauge) to 0.45 mm (26-gauge) external diameter) were measured and compared with the International Standard (ISO 7864-1984 E). The in vitro *performance of the needles was assessed by comparing times to appearance of cerebrospinal fluid and flow rates through the needles. There were wide variations in the measurements and performance of the different needles.*

The use of intrathecal drugs to produce either analgesia or anaesthesia has been limited, in part, by the problem of post-spinal headache. The headache, which may be disabling, has discouraged the use of "spinal anaesthesia", especially in younger patients in whom the incidence is said to be greater. However, the introduction of fine gauge needles has decreased the risk to less than 1% with 0.5-mm (25-gauge) and 0.45-mm (26-gauge) needles (Bonica, 1970).

One problem in using fine gauge needles (especially for the inexperienced operator) is visualization of the free-flow of cerebrospinal fluid (CSF) to confirm the position of the needle tip in the subarachnoid space. The only previous study which examined the *in vitro* performance of spinal needles (Messahel, Robinson and Mathews, 1983) found considerable differences in flow through two types of 0.5-mm (25-gauge) needle.

We have related the dimensions of some currently available spinal needles (0.7-, 0.5- and 0.45-mm; 22-, 25- and 26-gauge) to CSF flow at "high" and "low" pressures (equivalent to the sitting and lying positions for lumbar puncture). We have used the term "time to appearance of CSF" in an attempt to quantify how long the operator may expect to wait, under ideal conditions, before seeing a fluid meniscus within the needle hub.

In 1984 an International Standard for hypodermic needles was published and defined specifications in terms of metric measurements. This replaced the British Standard of 1976 which used British Standard Wire Gauge (BSWG) as its designated measurement. We have used metric units, and given the old British Standard size in parentheses.

MATERIALS AND METHODS

Fourteen different types of spinal needle, with external diameters in the range 0.7–0.45 mm (22–26-gauge), which are currently available in the U.K., were assessed (table I).

The internal and external diameters of 10 needles of each type were measured before they were divided into two groups of five to measure CSF flow at either high or low pressure. All needles were of a standard 90-mm length.

TABLE I. *List of needles studied. O = opaque hub; C = clear hub*

Manufacturer	External diameters (mm)		
Steriseal	0.7 (O)	0.5 (O)	0.45 (O)
BD	0.7 (C)	0.5 (O&C)	0.45 (C)
Monoject	0.7 (O)	0.5 (O)	
Spinocan	0.7 (C)	0.5 (C)	
Vygon	0.7 (C)	0.5 (C)	
Everett	0.7 (O)		

S. P. GERRISH,* M.B. B.CH., F.F.A.R.C.S.; J. E. PEACOCK,† M.B. CH.B., F.F.A.R.C.S.; Department of Anaesthetics, Northern General Hospital, Herries Road, Sheffield S5 7AU Accepted for Publication: May 7, 1987.

Present addresses:

*Department of Anaesthetics, Royal Hallamshire Hospital, Glossop Road, Sheffield S10 2JF.

†University Department of Anaesthetics, Sheffield University Medical School, Beech Hill Road, Sheffield S10 2JF.

Dimensions

Measurements were made at the tip (across the bevel) using a measuring microscope incorporating a micrometer screw-gauge. The internal diameter was taken as the difference between two readings made in a plane perpendicular to the length of the needle and tangential to the curves of the inner wall of the needle. The external diameter was measured in a similar way, using the outer surface of the bevel.

CSF flow

An *in vitro* model was used to measure CSF flow. A fluid filled reservoir was connected by large bore tubing and a three-way tap to a self-sealing bung for needle insertion. A simple liquid manometer was attached to the third port of the three-way tap. The pressure in the system was altered by adjusting the height of the reservoir so that the reading on the manometer was either 12 or 50 cm of CSF, and thus equivalent to the lying or the sitting position.

The system was filled with an artificial CSF which had a chemical content and viscosity similar to that of real CSF and physiological temperature (37 °C) was maintained by passing the connecting tubing through a water bath. Viscosities were measured using a Carrl-med controlled stress rheometer.

The time to appearance of CSF was measured by inserting the needle through the bung and starting a stop-watch as the stylet was withdrawn. The same two observers were used throughout the study to look down into the hub, or through the hub when it was transparent, until the CSF was first seen—at which time the watch was stopped. This first evidence of CSF within the hub—whether viewed through a clear hub from above or looking into an opaque hub—was defined as the "time to appearance of CSF". Five results were obtained for each needle type.

After the appearance time had been recorded, the CSF was collected and weighed continuously on an electronic balance. Readings were taken at 1-min intervals for 5 min for 0.7-mm (22-gauge) needles and 8 min for 0.45-mm and 0.5-mm (26- and 25-gauge) needles. Flow volumes at 1-min intervals were obtained for each needle by subtracting consecutive results. This produced four results for the larger, and seven for the smaller, needles because we discarded the result for the first 1 min to avoid differences attributable to appearance times. These results were then used to calculate the mean flows for the individual needles. Five results were obtained for each type of needle.

Analysis of variance was used to compare data from different groups of needles. Tukey's Honestly Significant Difference test was used to detect which pairs of needles within the groups were the cause of any significant difference. The Mann–Whitney *U* test was used to compare individual pairs of needle samples. Differences were considered statistically significant when $P < 0.05$. Two-tailed P values were obtained for the Mann–Whitney *U* test.

RESULTS

The results of the viscosity measurements performed on the different fluids are listed in table II.

Needle dimensions

There were major differences in dimensions between the needle types (fig. 1). The mean external diameter of the 0.7-mm Spinocan needle was significantly smaller than that of the Vygon and BD needles ($P < 0.05$).

The mean internal diameters of the 0.7-mm needles showed much larger differences between needle types. The mean internal diameter of the Vygon needles was significantly larger than all the other 0.7-mm needles ($P < 0.01$) and the Steriseal internal diameter was larger than the Monoject, Everett ($P < 0.05$) and Spinocan ($P < 0.01$) needles.

The results for the 0.5-mm needles showed that the Spinocan needles were of significantly greater external diameter than all the other needles ($P < 0.05$) except for the Monoject. The diameter of the Monoject needles tended to be larger than the

TABLE II. *Different fluid viscosities at different shear stress*

Shear stress (Pa^{-1})	Viscosity ($mPa\ s^{-1}$) CSF	 Artificial CSF	 Saline
0.84	0.88	0.82	0.76
1.69	0.84	0.81	0.76
4.21	0.78	0.81	0.76
8.43	0.78	0.80	0.76
10.11	0.78	0.80	0.76
12.64	0 78	0.79	0.76

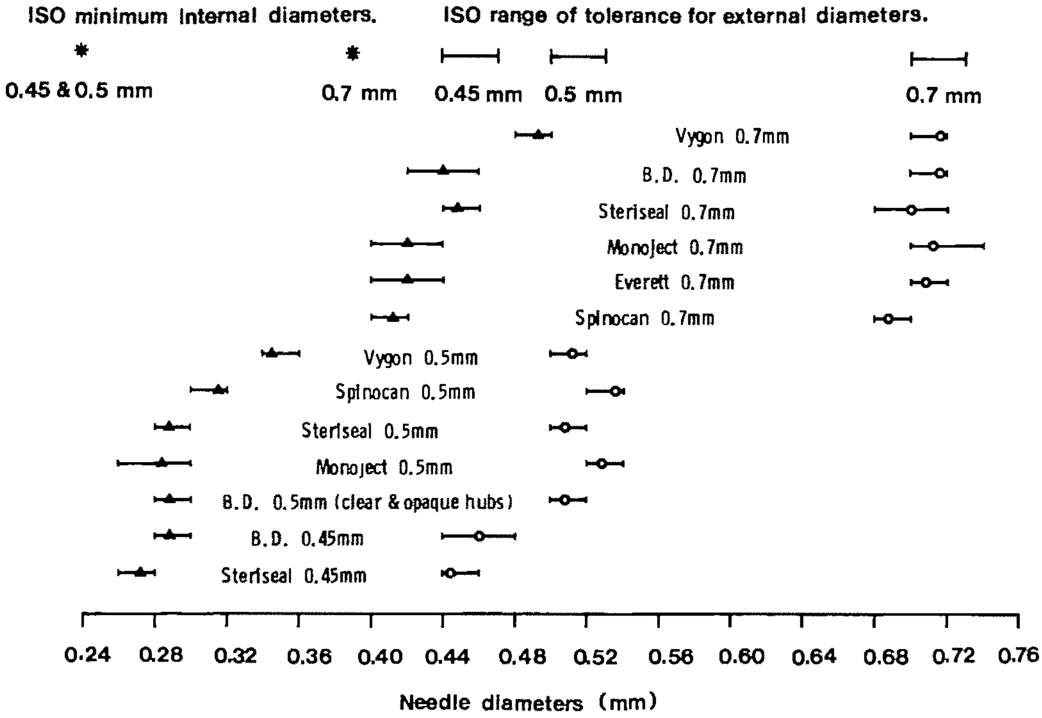

FIG. 1. Internal (▲) and external (○) needle diameters (mean and range) of the different needles tested with ISO specifications.

remaining needles, but the differences did not reach statistical significance. The external diameters of the 0.45-mm needles did not differ significantly.

The internal diameters of the 0.5-mm and 0.45-mm needles are considered together, because the ISO specifications for their internal diameters are identical. The Vygon 0.5-mm needle had a significantly larger mean internal diameter than all the other needles in the group ($P < 0.01$). The Spinocan needles were of significantly larger diameter than the remaining needles ($P < 0.05$, except for the Steriseal 0.45-mm needle: $P < 0.01$).

Time to appearance of CSF

The results are summarized in figure 2. Delay in appearance times occurred mainly in the smaller diameter needles at the lower pressure. All the needles had a significantly shorter appearance time at the higher pressure ($P < 0.001$, except the Spinocan: $P < 0.01$). Some smaller diameter needles with clear hubs, for example the Vygon 0.5-mm, had shorter appearance times at the same pressure than the larger needles with opaque hubs, such as Monoject, Everett and Steriseal 0.7-mm needles ($P < 0.001$ at the lower pressure). Using pooled data, needles with clear hubs all had significantly shorter appearance times than needles of the same specified diameter with opaque hubs ($P < 0.001$). A direct comparison of the two forms of the BD 0.5-mm needles showed a significant difference between the two needles ($P < 0.001$).

CSF flow

The results are summarized in figure 3. There were no significant differences between the flows of individual needles of the same type at the same pressure. Each needle type had a significantly greater flow at the higher pressure ($P < 0.001$). The Vygon 0.5-mm needle had significantly faster flows than all the other 0.5-mm needles at both pressures ($P < 0.01$) and the Spinocan 0.5-mm had faster flows than all the remaining 0.5-mm needles at both pressures ($P < 0.01$). The Vygon 0.7-mm needle also had greater flows at both pressures than the other 0.7-mm needles ($P <$

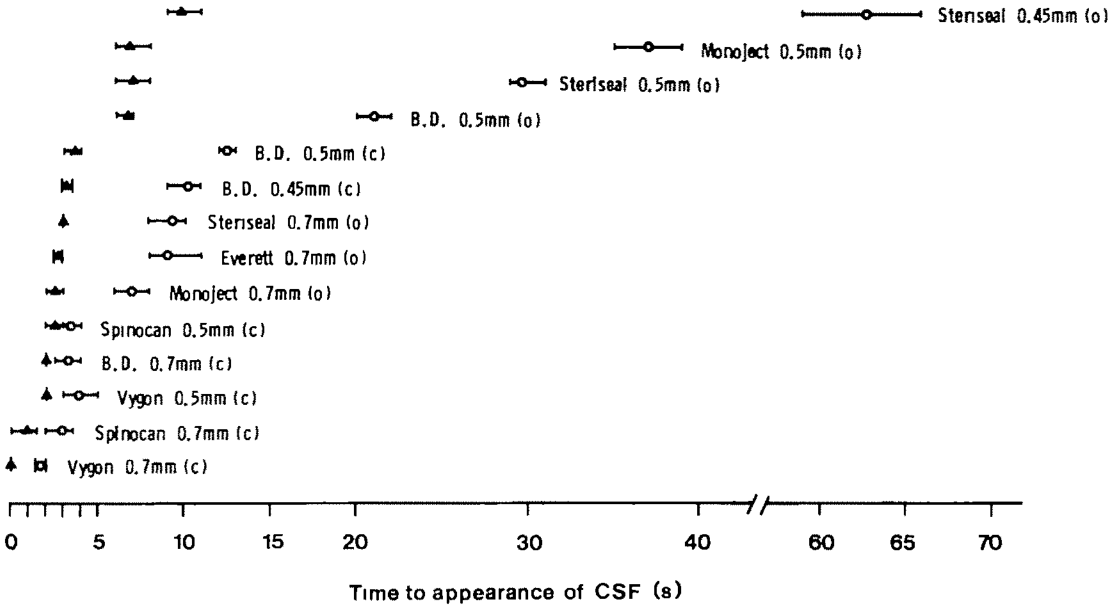

FIG. 2 Time to appearance of CSF (mean and range) measured at 50 cm CSF (▲) and 12 cm CSF (○) pressure for the different needle types.

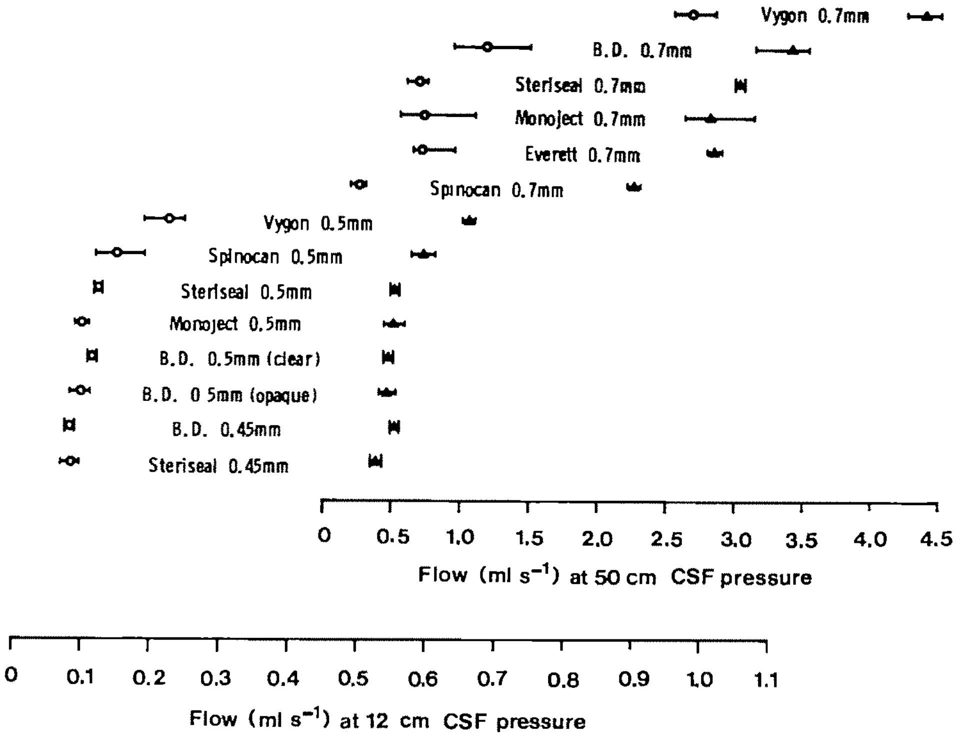

FIG. 3 Flow related to needle types (mean and range) at 12 cm CSF (○) and 50 cm CSF (▲) pressure.

0.01), but the 0.7-mm Spinocan had significantly slower flows than all the other 0.7-mm needles at both pressures ($P < 0.01$).

DISCUSSION

We have compared the dimensions and *in vitro* flow rates of different spinal needles using artificial CSF and a system that would mimic the clinical situation.

The viscosity measurements (table II) showed that, while saline is a Newtonian fluid, the two forms of CSF are not. Although the artificial preparation is not identical to real CSF, its viscosity is closer to it than is saline.

Variation in the diameters of needles from different manufacturers was documented by Messahel, Robinson and Mathews (1983) when they compared the BD and Spinocan 25-gauge needles. They suggested that the differences were the result of the manufacturers using different standards and they thought that an International Standard should be produced to avoid this problem. An International Standard is now available (ISO 7864-1984 E) and defines the specifications in terms of metric equivalents of the previously used gauge sizes. The differences between the last British Standard (BS 5081 1976) and the International Standard are shown in table III.

Any conclusions drawn from our results must take into account two additional factors: the permitted tolerance within the standard used and the accuracy of our measurements. The diameters were obtained by subtraction of two measurements which may produce a doubling of the error of each individual measurement. Hence an accuracy of 0.005 mm in each individual measurement could produce an error of 0.01 mm for any needle diameter. All the mean external diameters measured were within 0.01 mm of the quoted standard tolerance. However, the mean diameter of the Spinocan 0.5-mm needles was larger than the tolerances allowed by the International Standard. Messahel, Robinson and Mathews (1983) showed that the Spinocan 0.5-mm needles were larger than the BD 0.5-mm needles, which is consistent with the results that we have obtained. The mean external diameter of the Spinocan 0.7-mm needle was smaller than the tolerance quoted in the International Standard. Although individual needles from the Monoject 0.7-mm and 0.5-mm and the BD 0.45-mm samples had measurements greater than the permitted tolerance, the results were not statistically significant and the mean values of the needle samples all lay within the range of tolerance. Similarly, the Steriseal 0.7-mm sample had a measurement smaller than the quoted tolerance, but the mean result lay within the range of tolerance.

The differences in external diameters demonstrated in the present study can be explained in one of two ways. Either the manufacturer is working to an outdated standard now that the International Standard is available, or the manufacturers' specifications or tolerances do not match those of the International Standard.

Most needles are supplied with the needle size marked on the outer packaging. This may be in metric or BSWG units. On the basis of our results

TABLE III. *Comparison of external diameter measurements using ISO and SWG standards, and ISO tolerances for internal and external diameters*

	International Standard: nominal external diameter (mm)				
	0.45	0.5	0.6	0.7	0.9
Equivalent standard wire gauge (SWG)	26	25	23	22	20
Metric conversion of SWG (mm)	0.457	0.508	0.610	0.711	0.914
ISO tolerances (mm)					
External diameter					
Minimum	0.44	0.50	0.62	0.70	0.86
Maximum	0.47	0.53	0.65	0.73	0.92
Minimum internal diameter (mm)	0.24	0.24	0.32	0.39	0.56

it would seem possible that an operator could use a needle larger or smaller than that consistent with the International Standard. This may be the result of different manufacturing standards or individual needle variation. Since spinal headaches are related to needle size, this may produce increased morbidity, since the needle would be larger than anticipated.

The differences in internal needle diameter between the different needle types are of less consequence when related to the International Standard, because only a minimum diameter is quoted and not a range, as for external diameter. All the needles measured exceeded this value. Although related to the external diameter of the needle, the internal diameter is also related to the thickness of the needle wall. The manufacturer must balance the increased flow with a thinner wall needle against a more rigid needle with a thicker wall. Only one manufacturer seems to have moved towards creating a thin-wall needle. Vygon needles had significantly larger internal diameters than other needles of the same specified external diameter. The 0.5-mm Spinocan also had a larger internal diameter, but this would seem to be related to its larger external diameter.

Each needle was used only once because reinsertion of the stylet may produce metal shards. In addition, examination of used samples revealed the presence of crystalline material within the needle and this might have produced erroneous results with re-use. The material was thought to be a deposit of substances such as protein from the artificial CSF used in the study. It was most noticeable after the liquid had dried out, but we felt that differences would occur even after a single use. In consequence, repeated measurements were not made on individual needles and tests could not be applied to look for variation in appearance times within an individual needle. By weighing the CSF at 1-min intervals, we obtained a series of CSF flow rates for each needle and these were used to assess differences in CSF flows within needle types.

The results showed the prolonged period of time (up to 66 s) which may elapse before a fluid meniscus is seen when small diameter needles are used. This was particularly noticeable in needles with opaque hubs at the lower pressure. Clear hub needles allowed a shorter appearance time and may be useful for more rapid assessment of successful dural puncture. An alternative method may be to aspirate gently as advised by Slattery, Rosen and Rees (1980). The additional advantage of both these methods is that the colour of the fluid can be identified to help avoid the possibility of i.v. injection. The shorter appearance times with the clear hub needles is effectively a perceptual phenomenon, as can be seen from the comparison of CSF flow in the two types of 0.5-mm BD needles, where there was no significant difference ($P > 0.05$). The use of such needles may aid the inexperienced operator and avoid unnecessary multiple attempts at dural puncture.

The differences in CSF flow that are documented would appear to be related to the internal diameter, because the order of ranking for the internal diameters is similar to that for the rates of CSF flow (table IV). However, simple calculation (assuming laminar flow) using the product of measured flow and the fourth power of the internal diameter, which should be constant for the same fluid and pressure gradient, showed that this was not the complete picture. Messahel, Robinson and Mathews (1983) found considerable differences in the finish of the internal surface of the two needle types they examined and suggested that this may have a marked effect on fluid flow. Although we did not perform longitudinal sections in this study, we found, on microscopic examination of the needles for measurement purposes, that some needles had a relatively smooth finish and others had a considerably rougher finish on the internal surface. Although the major factor in CSF flow is the internal diameter of the needle, the quality of finish of the internal surface may also be important, since it may result in non-laminar flow. This may explain the differences in flow between certain needles, for example 0.7-mm BD and Steriseal needles, where the ranking for flow and internal diameter is reversed.

In conclusion, the study confirms and extends the previous work of Messahel, Robinson and Mathews (1983) and shows the considerable differences that exist between the various needles available. In the hands of an experienced anaesthetist, it would probably make very little difference which needle was used, but for the novice the help given by using the sitting position and being aware of the potential differences in needle performance may help decrease the morbidity associated with dural puncture.

TABLE IV. *Rankings and measurements for internal diameters and flows at 12 cm CSF pressure for all needles*

Internal diameter			Flow at 12 cm CSF pressure	
Rank	Needle	Size (mm)	(ml s^{-1})	Rank
1	Vygon 0.7	0.492	0.986	1
2	Steriseal 0.7	0.448	0.588	5
3	BD 0.7	0.440	0.679	2
4	Monoject 0.7	0.420	0.597	3
5	Everett 0.7	0.420	0.591	4
6	Spinocan 0.7	0.412	0.501	6
7	Vygon 0.5	0.344	0.226	7
8	Spinocan 0.5	0.316	0.148	8
9	Steriseal 0.5	0.288	0.122	9
10	BD 0.5	0.288	0.116	10
11	BD 0.45	0.288	0.082	13
12	Monoject 0.5	0.284	0.103	11
13	Steriseal 0.45	0.272	0.084	12

ACKNOWLEDGEMENTS

We are grateful to Mr T. Moore for the preparation of the artificial CSF, to Dr D. Northcliffe for measuring the viscosities and to Dr J. Alderson and Professor W. Nimmo for their help and advice.

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DANGERS OF ANAESTHESIA IN MUNCHAUSEN'S SYNDROME

R. A. S. FRATER AND J. K. L. LEW

SUMMARY

Patients with Munchausen's syndrome often undergo multiple surgical operations under general anaesthesia. They tend to have multiple exposures to routinely used anaesthetic agents. A patient with Munchausen's syndrome who developed an anaphylactoid reaction to thiopentone is described and the importance of obtaining previous case notes is stressed.

Patients with Munchausen's syndrome (Asher, 1951) have frequently undergone a variety of surgical operations at different hospitals, and will have received numerous anaesthetics. It is a unique feature of anaesthesia that short-lived adverse reactions may be unknown to the patient, but will be recorded in the anaesthetic notes. Even if these reactions are known, such patients may be reluctant to divulge the information, fearing discovery. Thus, if there has been an anaphylactoid reaction to a previous anaesthetic agent, the patient may be at considerable risk of having a fatal reaction subsequently, especially if he presents for emergency surgery which is carried out without reference to previous notes.

CASE REPORT

A 57-year-old prisoner was admitted to hospital with a 24-h history of pain in the left groin and flank associated with haematuria. The pain had increased in severity since its onset, but had been eased by pethidine, given before admission. He gave a past history of appendicitis, perinephric abscess, and perforated duodenal ulcer, all requiring surgery. He also reported chronic bronchitis. He was taking no medication, but claimed allergy to pethidine. He described breathlessness on moderate exertion and orthopnoea, but denied symptoms of angina pectoris. He smoked four cigarettes per day and reported a cough with clear sputum.

On examination he had scattered rhonchi in the chest and there were multiple scars on the abdomen. Tenderness in the left loin was elicited and blood was observed to be oozing from the external urethral meatus. Investigations during the first 24 h included an i.v. urogram which showed "excretion of dye by both kidneys with no ureteric dilatation".

After 24 h observation, in view of the persistence of his symptoms, cystoscopy was planned. During the preoperative interview by the anaesthetist the patient denied problems associated with previous anaesthetics. There were no old notes available as all his operations had been carried out at hospitals in other cities. No premedication was prescribed, but he was fasted before surgery.

Anaesthetic sequence

Venous access was established and, following the induction of anaesthesia with fentanyl 75 mg and thiopentone 250 mg, there was acute cardiorespiratory collapse with rapidly deepening cyanosis. Manual inflation of the lungs proved difficult and became impossible as a result of severe bronchospasm. Suxamethonium 100 mg was given and orotracheal intubation performed. Artificial ventilation with 100% oxygen failed to reverse the central cyanosis and considerable

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R. A. S. FRATER,* M.B., CH.B., F.F.A.R.C.S; J. K. L. LEW,† M.B., CH.B., F.F.A.R.C.S; University Department of Anaesthesia, Leicester Royal Infirmary, Leicester LE1 5WW. Accepted for Publication: July 7, 1987.

*Present addresses:

*Department of Anaesthesia, South Cleveland Hospital, Marton Road, Middlesbrough, Cleveland TS3 4BW.

†Department of Anaesthesia, Edinburgh Royal Infirmary, Edinburgh EH3 9YW.

Correspondence to J.K.L.L.

bronchospasm persisted. The pulse became difficult to feel and multiple ventricular extrasystoles were noted on the ECG monitor. Ventricular tachycardia developed and this rapidly deteriorated to coarse ventricular fibrillation. External cardiac massage was performed and the ventricular fibrillation antagonized with a single d.c. shock of 200 J, after which sinus rhythm returned, being maintained at 130–140 beat min^{-1}. The patient's colour improved, although the wheeze persisted and he developed a widespread maculopapular rash. Hydrocortisone 200 mg and chlorpheniramine 10 mg were given. Thereafter, the patient started to gag on the tracheal tube, making some ineffective breathing movements. He was given diazepam 10 mg i.v. and was transferred to the intensive care unit. His wheeze and skin eruption resolved within a few hours. The artificial ventilation was discontinued and the trachea extubated the following morning. He developed a cough and mucoid sputum for a few days, but there were no neurological or cardiac sequelae.

Cystoscopy and retrograde pyelography were performed under uneventful spinal anaesthetic 10 days later; no abnormality was seen.

The patient was subsequently discharged after having been told about his anaphylactoid reaction. He was also issued with a Medic Alert bracelet. Following the acute incident, his wife was contacted and informed us that her husband had often been in hospital and had indeed been "blacklisted" by one hospital. We were able to trace notes from four different hospitals where the diagnosis of Munchausen's syndrome was made, and assembled the following relevant facts:

1969: IVP. No radiographs taken because, following injection, "the patient appeared shocked".

1969: General anaesthetic for cystoscopy. "Patient unco-operative". Thiopentone induction.

1970: Rash following erthromycin.

1973: Rash following ampicillin.

1973: General anaesthetic for cystoscopy. Thiopentone, atropine, diazepam at induction. No adverse comment.

1975: General anaesthetic for laparotomy. Thiopentone, atropine, suxamethonium, pancuronium. Pronounced bronchospasm.

During this admission, he presented with a history of probable ingestion of a foreign body and abdominal pain. A plain abdominal radiograph showed a staple, but laparotomy and peroperative radiographs failed to confirm this, resulting in a suspicion of fabrication.

1978: General anaesthetic for cystourethroscopy. Thiopentone, suxamethonium at induction. "Developed bronchospasm".

Investigations

Blood was taken in the anaesthetic room and serially in ITU during the 12 h following the incident. These were analysed at the Supraregional Protein Reference Unit at Sheffield. IgE was slightly higher than normal at 120 u ml^{-1}; the concentrations of plasma complement and the other immunoglobulins were normal and were unchanged in the serial blood samples, indicating lack of involvement in the reaction.

Skin prick tests were carried out as outpatient procedures 4 months later with positive responses to thiopentone at 1/100 and 1/10 dilutions and no response to fentanyl 1/10. There was no response to either drug in a control subject.

DISCUSSION

The exact mechanism of this adverse reaction is not clear. There may have been a non-specific release of histamine or other vasoactive substances not involving complement, or this may represent a type I hypersensitivity reaction involving IgE bound to mast-cells. The skin prick test is suggestive of the latter. There was no history of atopy, but previous exposure to thiopentone had provoked bronchospasm on two occasions—information which was not available at the time of administration of the recent general anaesthetic.

Munchausen's syndrome takes many forms (Asher, 1951; McDonald, Kline and Billings, 1979; O'Shea et al., 1984) and our patient demonstrated a past history of what Asher (1951) named "laparotomophilia migrans" and a presumed recent history of "haematuria histrionica". A history of imprisonment is common amongst Muchausen patients, and in our case this took him well away from hospitals he had previously attended. The urgency of his condition meant that anaesthesia for his cystoscopy was undertaken before notes relating to his previous operations had been obtained. The anaesthetic records would have revealed two previous adverse reactions to thiopentone and also difficulties during induction. Certainly, this knowledge would have altered our anaesthetic management.

The patient who suffers an adverse reaction to an anaesthetic agent may be unaware of its occurrence if the symptoms resolve before recovery, and if the anaesthetist does not inform him.

For all patients having an anaesthetic, it is important to obtain the previous admission notes and to review the anaesthetic records. As illustrated in the above case report, this is particularly true for the patient with Munchausen's syndrome who might have had numerous operations at various hospitals and who might not give a reliable history for fear of discovery.

ACKNOWLEDGEMENTS

We would like to thank Miss J. Bowcutt for her secretarial assistance. We are also indebted to Drs J. Watkin, A. R. Aitkenhead and D. Fell for their helpful comments.

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CORRESPONDENCE

COMBINATION OF FENTANYL, ETOMIDATE AND VECURONIUM MAY CAUSE SEVERE VAGOTONIC STATE

Sir,—Recent clinical reports have suggested that there may be a possible contribution of vecuronium to bradyarrhythmias (May, 1985; Milligan and Beers, 1985; Clayton, 1986; Pollok, 1986).

According to these reports, this kind of arrhythmia occurs in combination with the administration of vecuronium, mainly at the time of severe vagal stimulation such as manipulation of the peritoneum. It does not usually occur immediately after the induction of anaesthesia. Exceptions are the cases reported by Starr, Sethna and Estafanous (1986) in which the injection of vecuronium was combined with the rapid administration of large doses of sufentanil and caused asystole before intubation of during laryngoscopy.

According to our experience, asystole or severe bradycardia can occur even with light vagal stimulation and without large doses of opoid when vecuronium is administered together with etomidate and a small dose of fentanyl.

Out of 849 cases in which anaesthesia was induced with a small dose of fentanyl (0.003–0.004 mg kg^{-1}), etomidate (0.3–0.4 mg kg^{-1}) and vecuronium (0.1–0.12 mg kg^{-1}), we saw two cases of extreme bradycardia (less than 40 beat min^{-1}) before intubation, one while spraying lignocaine onto the patient's tongue and another during mask ventilation with oxygen. On occasions we saw extreme bradycardia or asystole during intubation (five patients), intraoral manipulation (one patient case) such as the insertion of fingers to the pharynx to aid the passage of a nasogastric tube, or through irritation of a nostril with a nasogastric tube (one patient).

These arrhythmias were relatively harmless, however, because in all of the above cases, the heart rate returned relatively quickly to greater than 40 beat min^{-1} when the manipulation was stopped and precordial thumps were given. In some instances atropine was injected. Our patients (mostly cardiac patients) are usually premedicated with diazepam 10 mg by mouth and morphine sulphate 0.15 mg kg^{-1} i.m., 1 h before the induction of anaesthesia. No atropine is given.

We could not find any definite correlation between specific cardiac diseases or preoperative medication and the occurrence of severe bradycardia or asystole. Arrhythmia occurred in patients with coronary artery disease as well as aortic or mitral valve disease. Some, but not all, patients were receiving β-blockers, digitalis or calcium antagonist before operation. It is particularly noteworthy that this kind of arrhythmia has so far never occurred when thiopentone 3–4 mg kg^{-1} or methohexitone 1–2 mg kg^{-1} was used, nor has it happened when pancuronium was substituted for vecuronium.

The possible mechanism for the haemodynamic differences between etomidate and barbiturate or between vecuronium and pancuronium is to be sought in their effects on vagal tone. In animal experiments, barbiturates have been shown to inhibit vagal activity, whereas etomidate was seen to have minimal effects or occasionally increase vagal activity (Inoue and Arndt, 1982). Pancuronium, but not vecuronium, has a vagolytic effect (Durant et al., 1979). Futhermore, it is tempting to speculate that vecuronium may contribute positively to the vagotonic response because vecuronium was shown to decrease heart rate in fentanyl anaesthesia (Salmenpera et al., 1983). Thus, when thiopentone, methohexitone or pancuronium is used, the vagomimetic effects of fentanyl are countered, but if this is not the case and the vagomimetic effects of fentanyl are enhanced by another agent, severe vagotonic reactions may result.

Vecuronium, which does not have autonomic or vagolytic effects, may be used to advantage, but its non-vagolytic effects may prove to be disadvantageous, as was shown in the patients of Starr, Sethna and Estafanous (1986) and in our patients. When one chooses to administer vecuronium to facilitate intubation one should take the combined use of vagolytic agents into consideration.

K. Inoue
W. Reichelt
Bad Oeynhausen

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A NEW DESIGN OF INTUBATING FORCEPS

Sir,—Nasotracheal intubation is often selected in paediatric patients—particularly infants requiring ventilatory support—in a wide variety of "medical" conditions and commonly in relation to major surgery.

Some paediatric units do not usually use the nasal route because of supposed technical difficulties. Supporters of the nasal route feel that the tracheal tube is more stable and secure,

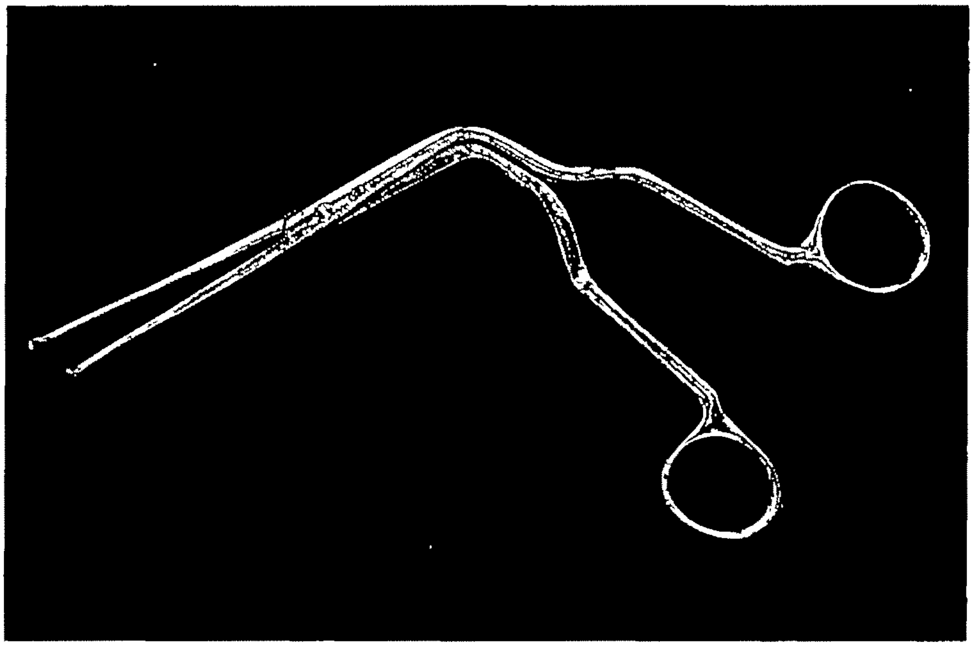

FIG 1. The new forceps, showing terminal "teeth".

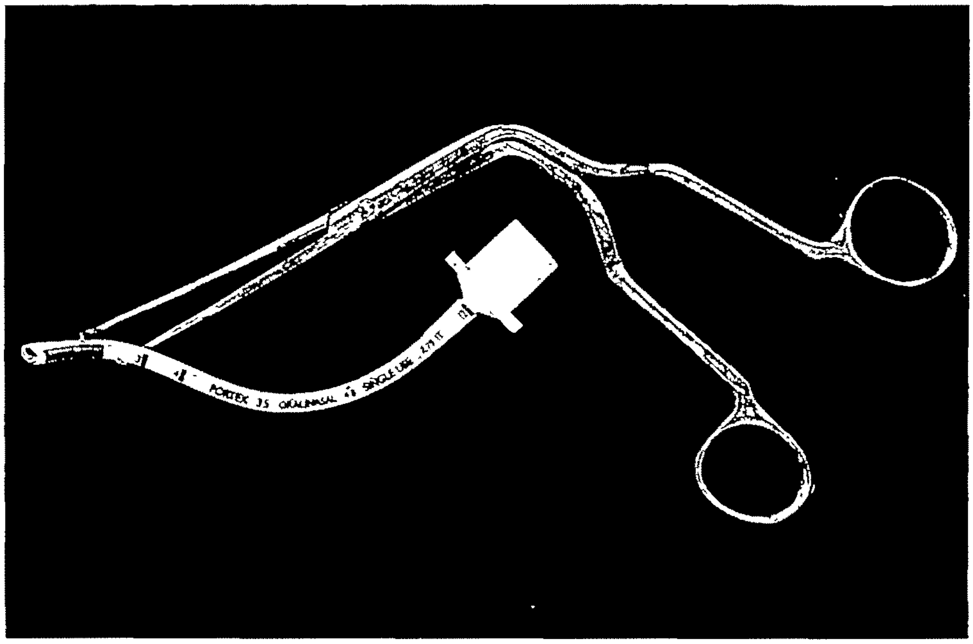

FIG. 2. The forceps gripping a tracheal tube

with less adhesive tape on the face; it also simplifies nursing care procedures.

The usual practice in nasotracheal intubation is to use Magill's forceps (which grip the tracheal tube from side to side), to lift the tip of the tracheal tube forward and to advance it into the laryngeal introitus, when it can be pushed on down the trachea.

It sometimes happens in adults, but more often in children in whom the larynx lies higher in the neck, that the tracheal tube will not run down the trachea. The usual remedy is, after removing the laryngoscope and forceps, to lift the head, flexing it on the neck, thus bringing the distal part of the tracheal tube more into line with the axis of the trachea, which runs downwards and posteriorly at an angle of 15°. The tube can usually then be pushed down. This manoeuvre is not under direct vision; sometimes the tracheal tube slips out of the laryngeal inlet and then it is the oesophagus that is intubated. The time that is taken to realize this error and reapply the mask may be critical in some very ill, or very cyanosed babies.

A new design of forceps has been made (fig. 1) in which two "teeth" protrude to the left and can grip the tracheal tube in front and behind. The teeth are so placed that closing the handles bends the tracheal tube backwards (fig. 2), and they are curved so that no size of tracheal tube will be flattened or kinked. The forceps are designed to be used in the sagittal plane.

In practice, the tracheal tube is pushed well down the pharynx and is grasped by rotating the forceps to hook the posterior tooth behind the tracheal tube. Care must be taken to avoid the uvula, a nasogastric tube or placing the posterior tooth into the side hole of the tracheal tube. The tracheal tube is lifted forward and the handles closed sufficiently to bend it backwards so that it can be advanced through the larynx under direct vision. The tracheal tube can then be fed through the larynx with the forceps, or an assistant can press the tube further in.

Apart from engaging the side hole of the tracheal tube which is very difficult to see, the writer has had no difficulties and no complications at all during many years use of the prototype instrument at the Royal Hospital for Sick Children, Edinburgh. These forceps facilitate intubation in critically ill babies, the whole process being extremely rapid and under direct vision. Oesophageal intubation is has not occurred.

The forceps can be used with all sizes of tracheal tube up to 6 mm bore. They are available from Northern Hospital Supplies Spylaw Street, Colinton, Edinburgh EH13 OJT.

R. Burtles
Edinburgh

RECOVERY AFTER ATRACURIUM

Sir,—A paper on the infusion of atracurium published in your journal (Sneyd, 1986) prompts me to make a plea for the routine use of anticholinesterase drugs after the infusion of non-depolarizing neuromuscular blocking drugs. Pharmacological antagonism was not used in 14 of the 15 patients studied, presumably because these patients "showed a normal response with no apparent reduction in train-of-four and no fade to tetanic stimulation" using a hand-held peripheral nerve stimulator applied over the facial nerve. Even if thumb adduction subsequent to supramaximal stimulation of the ulnar nerve is used, "it is difficult, and perhaps impossible, not only for inexperienced but also for experienced observers to visually and manually estimate a train-of-four ratio with sufficient certainty" (Viby-Morgensen et al., 1983).

A previous study which used accurate objective assessments of neuromuscular function during infusion of atracurium showed that the mean time from cessation of infusion to full spontaneous recovery was 42.2 min (Eager, Flynn and Hughes, 1984). The mean time from cessation of infusion to the end of the procedure in Sneyd's paper was 14.9 min. Although Eager, Flynn and Hughes (1984) studied longer infusion periods than Sneyd (1986) (range 128–233 min as opposed to 48–166 min), they used similar infusion rates (0.37 mg kg^{-1} h^{-1} compared with 0.3 mg kg^{-1} h^{-1}), and as spontaneous recovery rates from short infusions may not be significantly different from those receiving long infusions (Savarese et al., 1986), it is possible that Sneyd's patients had a small degree of residual paralysis which was not detectable with the methods he used. Patients who have received a small amounts of non-depolarizing neuromuscular blockers, and have small degrees of impairment of neuromuscular function, may experience unpleasant sensations associated with the use of the blocking drug (Howardy-Hansen et al., 1980; Engbaek et al., 1985).

Even though clinical assessment of the adequacy of ventilation and airway protection is judged satisfactory, patients who have received infusions of neuromuscular blocking drugs and in whom antagonism of paralysis is assessed by the clinical observation of the train-of-four response to peripheral nerve stimulation may, therefore, have sufficient residual paralysis to give rise to unpleasant subjective sensations in the post-operative period. I would, therefore, suggest that such patients should be given an anticholinesterase to prevent this.

A. W. Harrop-Griffiths
London

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Sir,—Your correspondent ignores the fact that the patients were tested with 50 Hz as well as a train-of-four. Assessment of tetanic response is easy and, in comparison with train-of-four "Sustained tetanic response must be regarded as more physiological and provides a more accurate indication of clinical recovery" (Eagar, Flynn and Hughes, 1984).

The average figure of 42 min for spontaneous recovery was based upon five patients who received a higher rate of infusion for a longer period than in my study. Of these, only one is fully documented, this patient was demonstrated to have a sustained head lift and a tidal volume greater than 400 ml within 4 min of the *onset* of ventilation.

All my patients showed a *sustained* tetanic response to 50 Hz stimulation *before* nitrous oxide was withdrawn. Elimination of nitrous oxide, extubation and recovery of conciousness all take some time, so further recovery of the neuromuscular junction would have occurred before the patient would be awake enough to experience the "unpleasant subjective sensation" to which Dr Harrop-Griffiths refers.

Howard-Hanson and colleagues (1980) and Engbaek and colleagues (1985) studied blocking drugs other than atracurium in awake preoperative patients and volunteers. To extrapolate their findings to sleepy postoperative patients is unwarranted.

Antagonism of neuromuscular blockade is not without risk (for example bradycardia and disruption of intestinal anastomoses). Following infusions of low dose *atracurium*, patients should be assessed with train-of-four *and* tetanic stimulation. Where clinical observation demonstrates satisfactory ventilation, airway protection and reversal of paralysis, I believe that antagonism is not essential.

J. R. SNEYD
London

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EXTRADURAL BLOCKADE AND INTRACRANIAL PRESSURE

SIR,—I am not qualified to comment authoritatively on the studies reported by Hilt, Gramm and Link (1986), although their results appear to accord with those of other workers to whom they refer. I do, however, take issue with some of the tentative conclusions drawn from these results by Hilt and colleagues and in your accompanying Editorial (Wildsmith, 1986).

We have in this service alone (and I am sure that we are not unrepresentative in this) administered a continuous lumbar extradural block for the labour of four women with benign intracranial hypertension and two with a space-occupying intracranial lesion, plus several who had been subjected to an intracranial surgical procedure. In none of these patients was there even a hint of an unwanted effect of any of the intra-extradural injections.

Of much greater moment is the question of pre-eclampsia. In common with many of this country and elsewhere, we consider the provision of extradural blockade—for labour or for Caesarean section—to be the outstanding technique of choice in the care of mothers with pre-eclampsia of any grade of severity. The contraindications are well known: the mother declines the offer; coagulopathy; severe hyper-reflexia suggestive of imminent eclampsia; rapidly increasing severity of fetal distress demanding immediate abdominal delivery. Many hundreds of pre-eclamptic mothers have been given extradural analgesia in our service. I have no evidence that there has resulted any instance of the complication under review, and I would be most reluctant to include such a complication in a list of potential hazards relating to the provision of an extradural block to a patient with pre-eclampsia. Of course I would accept that, if one were so unwise as to inject a large volume of anaesthetic solution (more than 10 ml, for instance) at one time, the possible resultant increase in intracranial pressure might lead to unpleasant sequelae (although we never saw even that in the "old days"), but that complication is of minor importance compared with the other potential hazards associated with such injudicious management.

J. SELWYN CRAWFORD
Birmingham

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INTRACRANIAL HYPERTENSION AND CAUDAL ANAESTHESIA

SIR,—I read with interest the valuable Editorial by Dr Wildsmith (1986) and the original article by Drs Hilt, Gramm and Link (1986). All stressed the relative contraindication of extradural anaesthesia in the presence of increased intracranial pressure (ICP) "..., not only because of the risk of tentorial herniation after accidental dural puncture, but also because of the risk of decreasing cerebral perfusion or aggravating brain shifts by increasing ICP." It was suggested that, perhaps, caudal analgesia would be a better technique (Crawford, 1978). However, we encountered two parturients with brain tumours who developed CNS complications after caudal analgesia (Abouleish, 1977). In those two patients the one-dose injection of 1.5% lignocaine 22 or 24 ml through a needle for forceps delivery resulted in apnoea, total loss of consciousness and severe bradycardia. The episodes lasted 5 or 6 min, respectively. Inadvertent intravascular injection was excluded, based on the absence of convulsions, and the presence of adequate analgesia, with T10 or T9 level of sensory block, respectively, and lasting for 90 min following the caudal injection.

The dural sac ends normally at the level of the second sacral vertebra — about 5 cm from the sacral hiatus. Thus the injection of a solution in the caudal canal supposedly affects the ICP less because of this distance from the subarachnoid space. However, with increased ICP, the dural sac may expand further down, and the rapid injection may transmit more pronouncedly than normal the increased pressure in the caudal canal to the subarachnoid space. Therefore, although on theoretical grounds caudal block is safer than extradural anaesthesia in patients with increased intracranial pressure, caution must be taken to minimize the increase in ICP by fractionating the dose to small volumes of 3 ml, injecting it over 5–10 min and observing the reaction of the patient to each injection. Another point that needs stressing is that, normally, the risk of dural puncture is less with caudal anaesthesia than with extradural anaesthesia. However, the distension of the subarachnoid space and possible expansion of the dural sac with ICP require more caution than usual. To avoid this problem, one should use a needle-cannula catheter to perforate the posterior sacrococcygeal ligament, and advance only the cannula once the ligament has been perforated (Owens, 1973).

E. Abouleish
Houston, Texas

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Sir,—We appreciate Dr Abouleish's comment on our article and the information about the two parturients developing CNS complications following caudal anaesthesia. This is stressing the problem pointed out in our article.

Furthermore, we agree completely with Dr Crawford that extradural anaesthesia is of outstanding value in the management of patients with pre-eclampsia but, as we discussed, there might be a risk of untoward effects in patients with compromised intracranial compliance. As we could demonstrate in our first patient, the extradural application of 10 ml, the upper limit mentioned by Dr Crawford, can lead to a dramatic increase in ICP. Even 5 ml induced a distinct increase in ICP. If, in these patients the extradural injection is not made with careful fractioning of the dose, as proposed by Dr Abouleish and concluded in our discussion, CNS complications might occur. The frequency of these untoward effects depends on the reduction of the intracranial compliance and the precautions taken.

Regarding the potential hazard, we conclude that extradural anaesthesia has to be administered with caution in patients with restricted intracranial compliance. In patients with intracranial pressure, so that others might avoid the problems method is contraindicated.

H. Hilt
H.-J. Gramm
J. Link
Berlin

Sir,—Thank you for letting me see the letters from Drs Crawford and Abouleish. The latter's case serves to support the view I expressed in the editorial, that extradural injections must be made slowly and with particular caution in a patient who may have an increase in intracranial pressure The second paragraph of Dr Crawford's letter demonstrates that these patients can still receive the benefits of a continuous extradural technique.

In response to Dr Crawford's third paragraph, all I can do is quote from my Editorial: "In a severely pre-eclamptic patient the benefits of extradural analgesia during labour are clear ...". The basic point of the editorial was to draw attention to the report that extradural injection can increase intracranial pressure, so that others might avoid the problems encountered.

J. A W. Wildsmith
Edinburgh

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BOOK REVIEWS

Problems in Obstetric Anaesthesia (*Perinatal Practice*, Vol. 3). Edited by B. Morgan. Published by John Wiley & Sons. Pp. 198; indexed; illustrated.

In their initial preface, the editors of the series (*Perinatal Practice*) state: "This series is offered as a contribution towards bridging the gap between obstetrics and neonatal medicine." They thus appear to overlook the important fact that anaesthetists and midwives are integral members of the "Perinatal team" too ! This regrettable omission is fortunately redressed by their commissioning of this volume (volume 3 of the series), *Problems in Obstetric Anaesthesia*, as stated in the second preface. From the outset therefore, this reviewer has no hesitation in expressing the opinion that this publication will prove "...of interest not only to anaesthetists, but also to obstetricians, paediatricians and midwives."

The book, in its express aim of directly addressing the perinatal team as a whole, achieves a gratifying measure of success. The usual problems of any multi-author publication are apparent in that both the quality of the individual presentations and use of language in the 13 chapters varies. This does not, however, detract significantly from the overall merit of the publication.

Chapters 2 and 3, "The Problems of Aspiration of Gastric Contents" and "Control of Gastric Acidity and Volume" overlap somewhat, and could logically have been amalgamated into a single chapter. They nonetheless cover the problems associated with the avoidance of aspiration pneumonitis methodically and well.

In chapter 4, "The Problems of Treating Shock in Obstetric Patients" are clearly presented in a rational manner by Gillian Hanson, a recognized expert in the field.

Chapter 7, "Severe Pre-eclampsia and Eclampsia", is marred only by the authors' rather one-sided (of the Atlantic) view. The proven value of i.v. magnesium sulphate in the clinical management of this perplexing syndrome, recognized by both obstetricians and anaesthetists practising in the United States of America and, indeed elsewhere in the world, is not even mentioned! Jim Pearson and Gareth Rees do, however, correctly highlight an often overlooked or forgotten fact, that the hypertensive mother remains at risk for 24–72 h after her delivery. They also, commendably, emphasize the major importance of an established unit management procedure for pre-eclampsia/eclampsia, to be followed in concert by all members of the perinatal team when confronted by a severely hypertensive parturient.

Chapters 8, "The Complications of Epidural Anaesthesia" by Trevor Thomas, and guest editor Barbara Morgan's presentation "Problems of Analgesia in Labour" (chapter 12), should be considered compulsory reading for the edification of all members of the perinatal team! The latter author rightly condemns the all too common but irrational practice of deliberate "failure to give continuing analgesia in the second stage of labour".

Donald Moir addresses the problem of "Anaesthesia and Maternal Death" (chapter 11) in his usual succinct manner, again defining the urgent need, so often overlooked by administrators, for a proper level of anaesthetic staffing in obstetric units if disasters are to be avoided. In addition, the requirement for a clearly enunciated failed intubation/ventilation drill is stressed, as well as the ready availability of a well equipped difficult intubation tray.

In the last chapter, entitled "Fetal and Neonatal Effects of Analgesic and Anaesthetic Drugs", the complexities of placental drug transfer and fetal pharmocokinetics are tackled in a commendable manner. Unfortunately, the results published by John Scanlon and his colleagues in 1974, which, for a time tarnished the image of lignocaine in the eyes of obstetric anaesthetists and anaesthetists both here and abroad, are given unwarranted attention. The figure appearing on page 186, reproduced with permission from a 1976 publication of Scanlon's, portrays findings that have since been clearly ascribed to the extradural use of mepivacaine alone, rather than lignocaine. Lignocaine has been tried and proven innocent many times over in recent years with regard to adverse effects on early neonatal neurobehaviour!

In summary, a useful book that should be available in labour suites and in respective departments to be read by obstetricians, paediatricians, anaesthetists, and midwives alike who participate in the regular care of the mother and child under the Perinatal Team banner

J. W. Downing

Oxygen Free Radicals in Shock Edited by G. P. Novelli and F. Ursini Published by Karger, Basel. Pp. 248; indexed; illustrated. Price £62.80.

This book is a compilation of abstracts presented, either verbally or as a poster, at the 1985 workshop on "Oxygen Free Radicals in Shock", held under the auspices of the European Shock Society. The 37 contributions vary widely in their length and content. For example, the early paper on granulocyte derived free radicals is 14 pages long and includes 60 well chosen references. This chapter is very comprehensive and easy to read. The shortest contribution is a three-page description of an HPLC method for measuring tissue peroxidation products in rat liver. By the nature of the book, each chapter can be read entirely on its own, the link between articles being simply that either or both oxidants and shock are included in the study.

Of the 37 papers, 10 are from eminent centres in the U.S.A. and Japan; the majority of these papers have appeared in refereed journals since this conference, and therefore would provide little new information to those interested in the role of free radicals in inducing tissue injury. Sixteen of the remaining 27 papers are from Italian centres, and four from Sweden. This may represent a bias resulting from the location of the conference and its sponsoring organization centre. There is only one paper from the United Kingdom.

Many of the contributions describe studies investigating basic mechanisms, usually performed in animals models. Systems studied vary from cell components (mitochondria and red cell membranes) to whole animal physiology. The stimuli to "shock" again vary from more standard infusions of endotoxin and hyperoxia in anaesthetized rats to experiments in which awake rats are subjected to 1–2000 revolutions in a tumbling drum. (A stimulus which is said to induce 100% lethality!)

Many of the papers describe studies in which antioxidant protection is given and include a number of studies using novel agents which may have promise, such as rosmarinic acid and various electron spin traps.

The book is extremely well presented and printed, but falls into the problem of being too advanced for the novice to the subject and having insufficient novel sections for those interested in oxidant injury. At the price it will probably find its way only into central library facilities, where it may provide a stimulus to further investigation. *D. Royston*

Head Injury and the Anaesthetist. Monographs in Anaesthesiology No. 14. Edited by W. Fitch and J. Barker. Published (1985) by Elsevier, Amsterdam, New York, Oxford. Pp. 278; illustrated.

Many anaesthetists either in established posts or in the training grades, whether they work in Neurosurgical Centres or not, will be required to take part in the management of head-injured patients at some time between the initial accident and their ultimate discharge from hospital. A book which is solely devoted to this subject should therefore be welcomed. The Editors have gathered a group of 12 contributors, most of whom come from Glasgow, but there are contributions from other centres in the United Kingdom, the United States and Hong Kong.

In the early chapters excellent reviews of the pathology and pathophysiology of head injuries and the associated alterations in pulmonary function are given. The initial assessment of the patient and his immediate care and transportation to a Neurosurgical Centre are then described, and there is a chapter devoted to reviewing the anaesthetic techniques used in anaesthetizing a head-injured patient. The subsequent chapters discuss the intensive care management of the head-injured patient, and the book concludes with a discussion of brain death, and probable future developments.

Each chapter includes a useful list of references for more detailed study, and the tables, figures and illustrations are clear.

Such is the development that has taken place in this field of medicine in recent years, that the reviewer feels that a revision of the text is now required. Indeed, the Editors have added additional references for 1984 and 1985 to the end of one chapter. If the book were revised and updated it would make essential reading for everyone involved in the management of head-injured patients. *J. L. Jenkinson*

Classical Anaesthesia Files. By D. M. Little jr. Published by Wood Library-Museum for Anesthesiology. Pp. 335; indexed. Price $35.

Over a period of 25 years (1955–1908), the late David M. Little jr made bi-monthly contributions to the Classical File of *Survey of Anesthesiology*. The trustees of the Wood Library-Museum of the American Society of Anesthesiologists regard these contributions as such a valuable legacy to those interested in the history of anaesthesia that they have collected them together in a single volume for preservation and availability. Little's aim was to reproduce seminal papers which led to landmark changes in the evolution of anaesthesia. Having identified these, he contributed introductory comments which are true masterpieces in both their style and their contents. For example, his introductions to papers by Priestley and Lavoisier give admirable summaries of the American Revolutionary War!

The articles are, for the most part, abridged,—a necessity forced on the Editing Sub-Committee in order to conserve pages. This is understandable, but nevertheless somewhat regrettable. However, every paper was a true original. The years of publication range from 1775 to 1967 and the writers from Wells, Morton and Simpson, through such as Guthrie, Bier and Sicard, to Beecher, Waters and Griffiths, to name but a few. It would seem that everyone and everything are here. The first external cardiac massage, defibrillation, trichloroethylene—wherever one turns one is overcome by the fascination of re-reading these remarkable pivotal papers, and to have them all in a single volume makes this book a veritable treasure house and a wonderful memorial to Little. No longer will frustrating hours have to be spent seeking missing papers or inaccurate references on the dust-laden shelves of medical libraries in order to settle such questions a "What did Mendelson actually describe in his syndrome?" or ""Who wrote the first paper on succinyl choline?" This book is an outstanding contribution to the literature of anaesthetic history and deserves to be read and reread. As such, it is not just a book to be recommended for libraries—it is one which should be in the personal possession of every anaesthetist.

P. W. Thompson

Muscle Relaxants: Side Effects and a Rational Approach to Selection. Edited by I. Azar. Published by Dekker, Inc. Pp. 238; indexed; illustrated. Price. $83.50.

Once upon a time, perhaps it was only 5 years ago, there was a need for a new monograph on muscle relaxants. Not since the definitive work by Katz (Excerpta Medica, 1975) had an attempt been made to review and update this subject. But then the tide turned: suddenly there was an influx of small books on this subject, each one part of a well recognized series of anaesthetic monographs. As the number increases, the need for any anaesthetist, even one interested in muscle relaxants, to obtain the lastest release probably decreases exponentially.

This book is a review of the side effects of neuromuscular blocking agents and the management of those patients in whom such agents must be used with extreme care. It is only an evening's reading and it is, therefore, perhaps unfortunate that this subject matter had not been combined with one of the other recently released monographs to produce a more substantive account of the state of play in the field. It is easy reading—nice paper, clear print—but space has been used too freely; why do we have to have subheadings at the beginning of every chapter? This must surely have helped push the price of this slim book up to more than £50.00.

Certain specialist areas have been covered well. A practical review of the diagnosis and treatment of Malignant Hyperpyrexia is given with utmost clarity. An update on the use of neuromuscular blockers in the burnt patient is also appreciated. The use of blocking agents in patients in renal or hepatic failure has been very topical since the advent of atracurium and vecuronium and we have it again here, but it is well written and, yet again, makes enjoyable reading.

Will those interested in neuromuscular blocking agents only live happily ever after if they purchase this book? I doubt it. It would be comforting, perhaps, to know it was on the shelves of the local medical library, but please, publishers, no more monographs on this subject until, at the least, we have another neuromuscular blocking agent! *J. M. Hunter*

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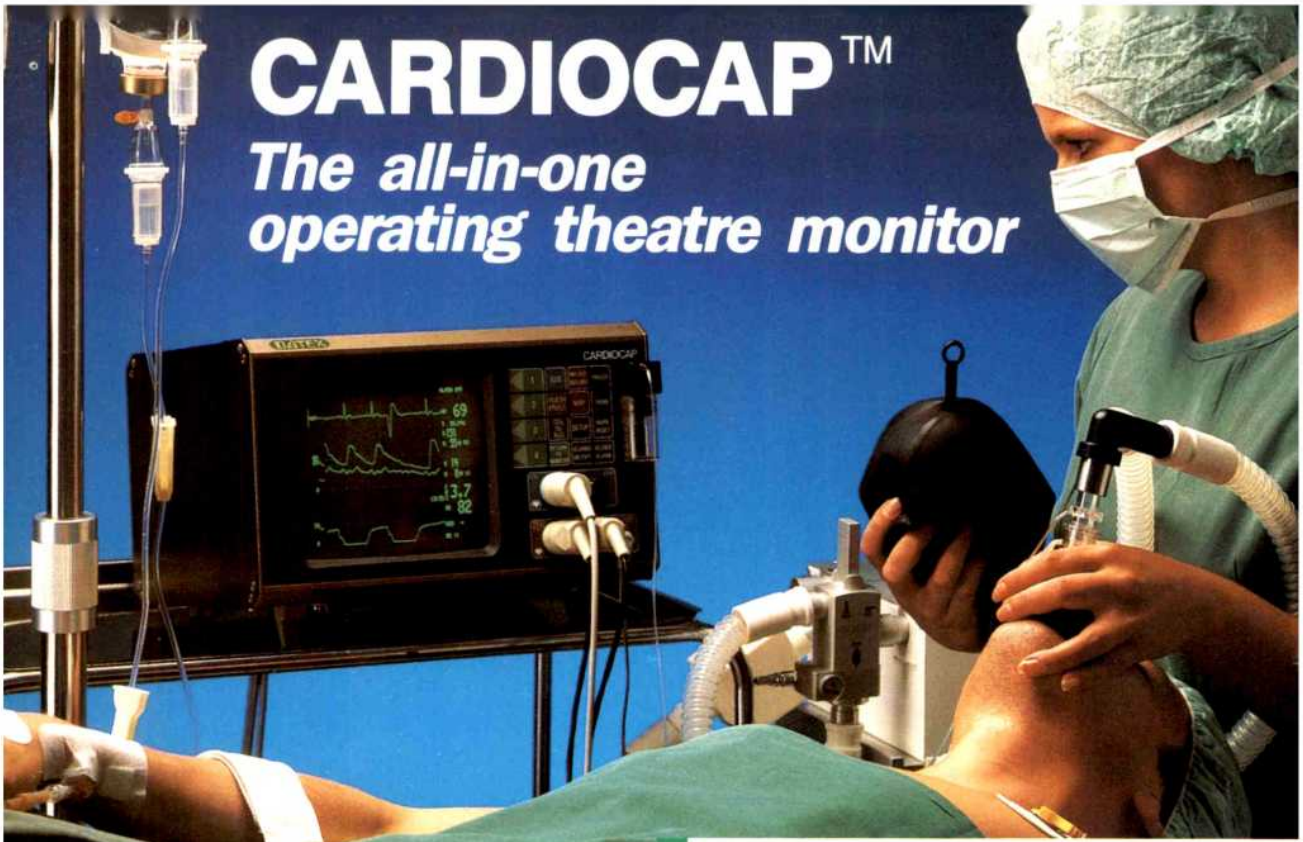

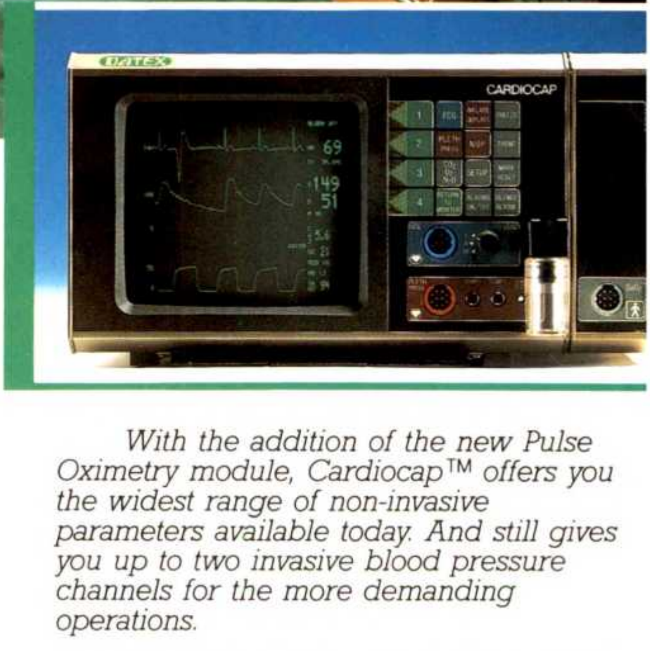

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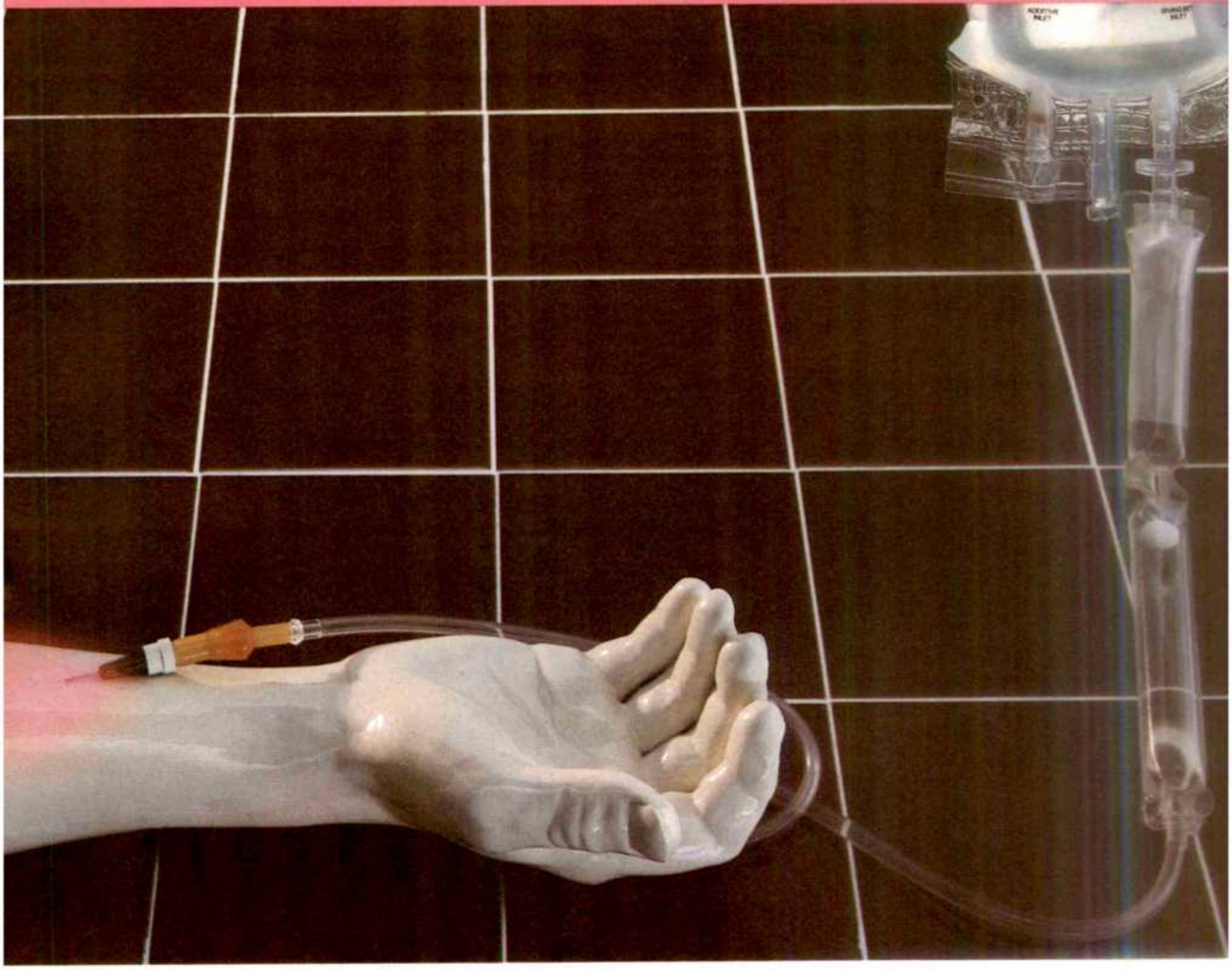

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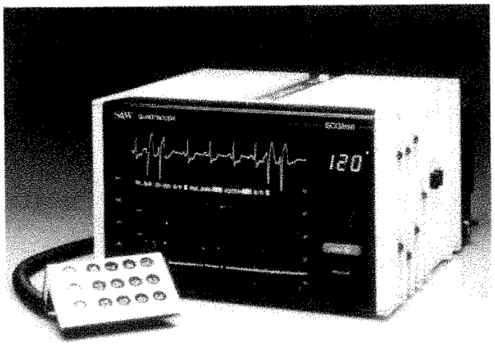

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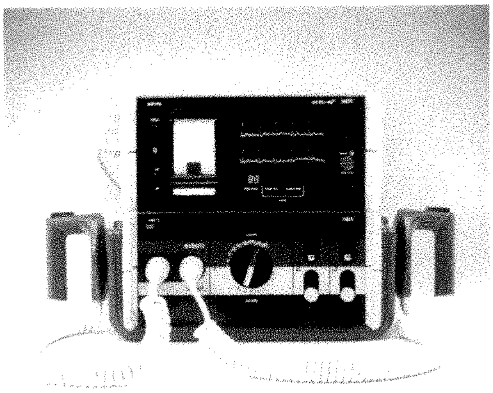

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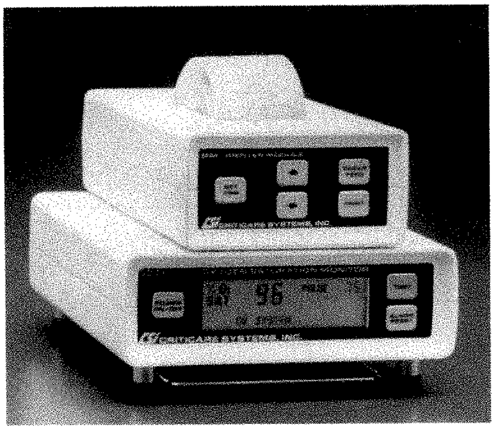

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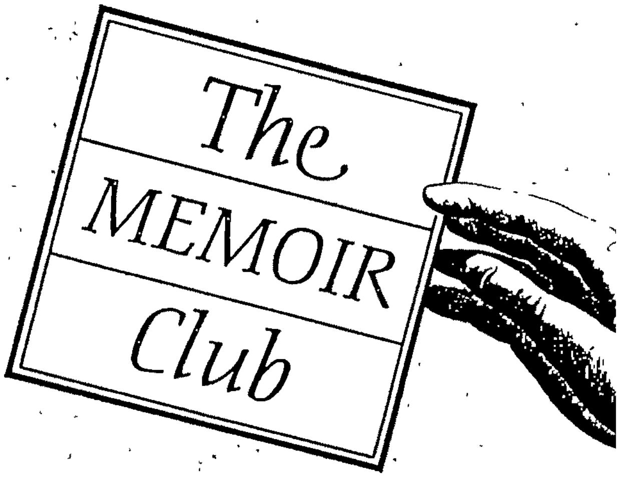

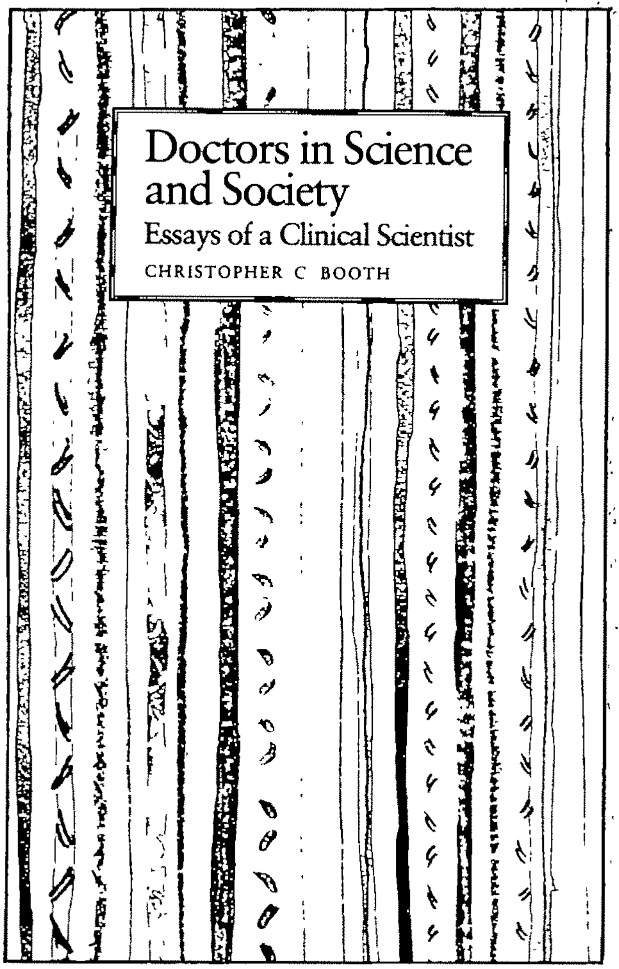

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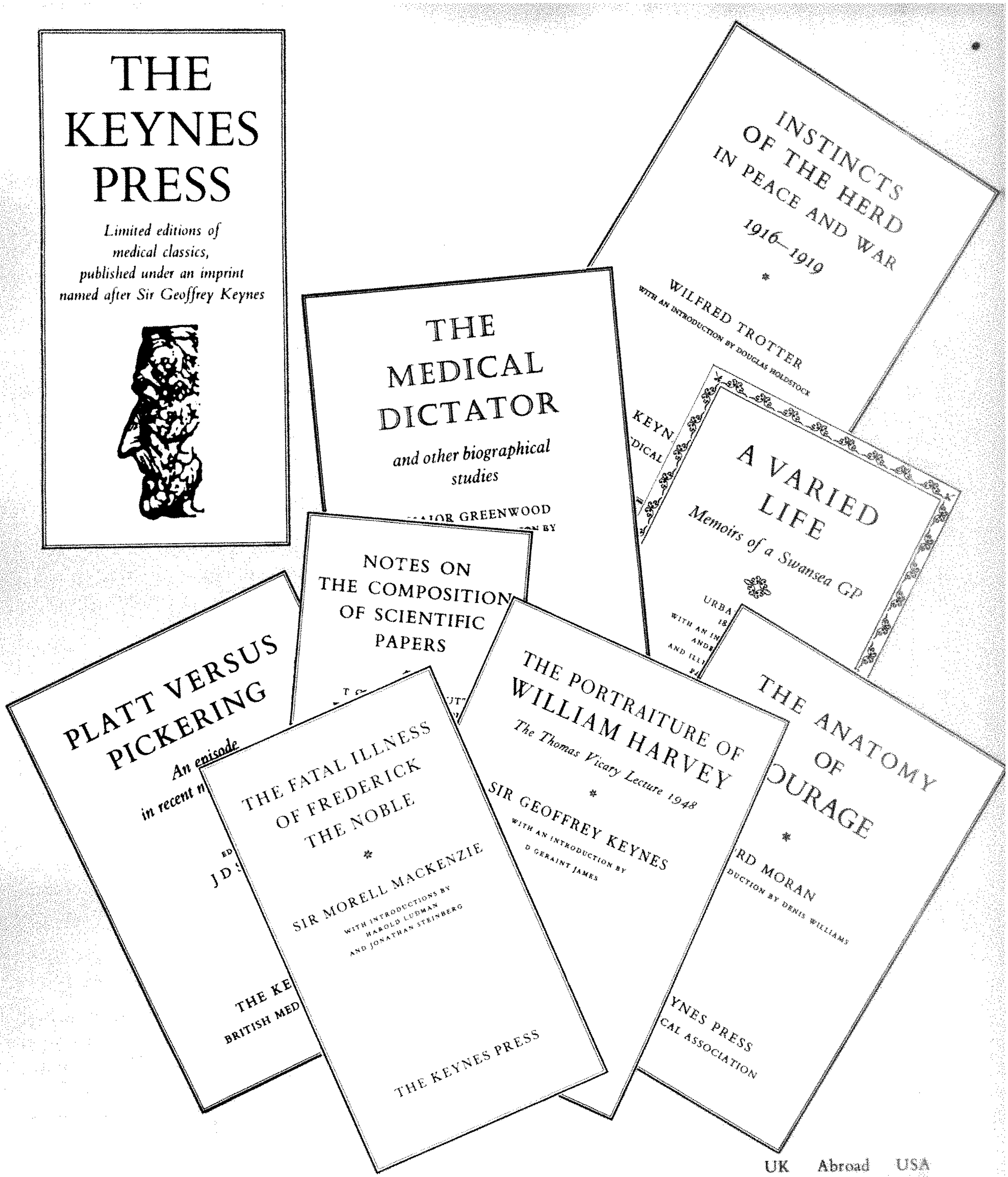
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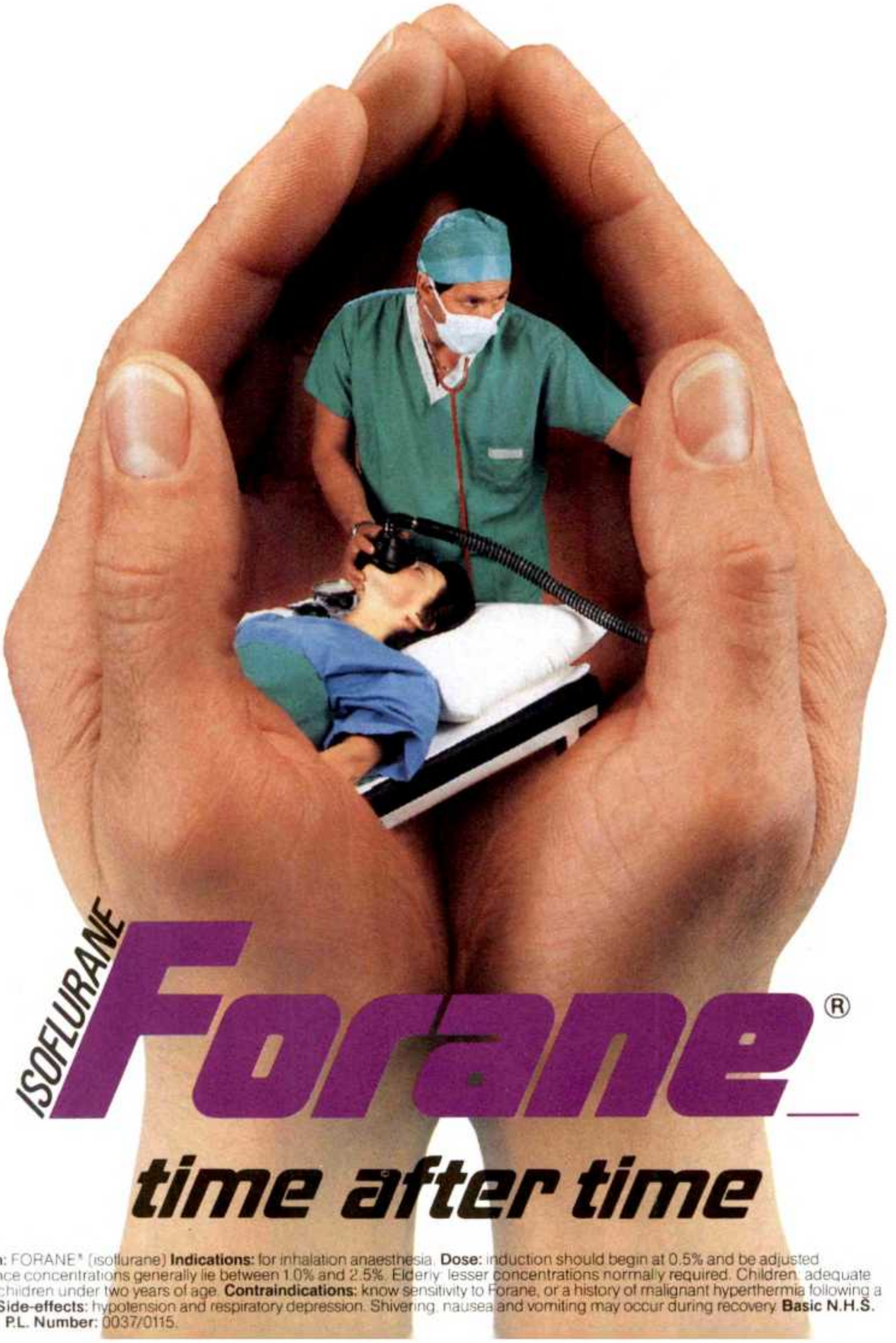

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W. RUSS, J. STICHER, H. SCHELD AND G. HEMPELMANN

SUMMARY

Somatosensory evoked responses after median nerve stimulation were recorded in 21 patients during hypothermic cardiopulmonary bypass. During hypothermia a significant linear correlation ($P < 0.001$) was found between evoked potential latency and temperature. Correlation was best for tympanic membrane temperature during cooling and for perfusate temperature (arterial, venous) during rewarming. The increase in latency was more pronounced for middle latency components (N_2, N_3) and for the early cortical N_1 than for the cervical N_0 and central conduction time. In all patients N_1 was detectable at 26 °C, with slightly reduced amplitude. In the rewarming period the changes occurred in the reverse order and pre-bypass values were achieved at normothermia. The slopes of the regression lines were different during cooling and rewarming, when latencies were related to patient (tympanic, nasopharyngeal, rectal) temperature, but identical when arterial or venous blood temperature was used as the reference. No correlation was found between latency and perfusion pressure. We conclude that sophisticated temperature measurement is required to aid the interpretation of evoked responses used during hypothermia.

Inadequate cerebral perfusion is a recognized hazard of cardiopulmonary bypass (CPB). Brain dysfunction may vary from slight neuropsychological disability to complete infarction of a hemisphere and contribute to the overall morbidity following CPB (Kolkka and Hilbermann, 1980; Savageau et al., 1982).

Advances in the monitoring of haemodynamic and respiratory variables have led to improvements in the management of patients undergoing open-heart surgery and increased the margins of safety. Monitoring of cerebral function, on the other hand, is not used routinely, despite recent advances in computer technology.

Various methods of computerized electroencephalography have been proposed; most have been reviewed by Levy and co-workers (Levy et al., 1980; Levy, 1984a, b). Despite computerized data reduction, interpretation of the different EEG descriptors such as spectral edge frequency (Homer and Stanski, 1985), peak power frequency or median power, remains difficult, especially under the influence of anaesthetic agents and hypothermia (Levy, 1984a).

Recording of evoked potentials is used widely as a neurophysiological means of investigating peripheral and lemniscal pathways up to the sensory cortex (Chiappa and Ropper, 1982a, b). Considering the distribution of the cortical evoked potentials for visual, auditory (Kileny, Dobson and Gelfand, 1983; Thornton et al., 1986) and somatosensory stimulation, much of the cortical surface is available for monitoring. Evoked potentials, particularly those of short latency, like the brain stem auditory evoked potential (BAEP) and the short-latency somatosensory evoked potential after median nerve stimulation (SEP), provide information about cerebral function even when the EEG is completely suppressed by anaesthetic agents (Newlon et al., 1983; Drummond, Todd and U, 1985).

WOLFGANG RUSS, M.D., JOCHEN STICHER, M.D., GUNTER HEMPELMANN, M.D. (Department of Anesthesiology and Intensive Care Medicine); HANS H. SCHELD*, M.D (Department of Thoracic and Cardiovascular Surgery); Justus Liebig-University of Giessen, Klinikstr. 29, D-6300 Giessen, Federal Republic of Germany. Accepted for Publication: March 11, 1987.

Correspondence to W.R.

The original waveforms are present, with delayed latency, during hypothermia, depending on the type of potential used. However, the effect of hypothermia has to be established in a quantitative manner, and the temperatures to which the EP-variables should be related during hypothermia have yet to be defined under clinical conditions. The study presented contributes to these basic considerations for EP monitoring during hypothermic cardiac surgery and describes the correlation of different variables of the median nerve SEP with temperature.

PATIENTS AND METHODS

Twenty-one patients (19 male) aged 51–69 yr (mean 58 yr) undergoing coronary artery bypass grafting gave informed consent. Ethics committee approval was obtained.

Patients were premedicated with morphine 10 mg and flunitrazepam 0.02 mg kg^{-1} given i.m. 60 min before the induction of anaesthesia. Central and peripheral venous and arterial cannulae were placed and electrocardiographic monitoring was initiated before the induction of anaesthesia. After induction with etomidate, anaesthesia was maintained with fentanyl 50 µg kg^{-1} and flunitrazepam 30 µg kg^{-1}. Neuromuscular blockade was achieved with repeated doses of pancuronium. Management of extracorporeal circulation (ECC) was standardized with a pump flow of 2.4 litre min^{-1} m^{-2}. Arterial pressure during ECC was kept between 50 and 100 mm Hg, with a perfusion pressure ($p_{art} - p_{ven}$) always greater than 40 mm Hg. Oxygenation was performed with a Travenol bubble oxygenator and controlled by repeated blood-gas analyses. For evaluation of temperature, temperatures in the venous (t_{ven}) and arterial line (t_{art}) of the oxygenator, and rectal (t_{rec}), nasopharyngeal (t_{np}) and tympanic membrane temperatures (t_{ty}) were recorded continuously with special thermistor probes (Yellow Springs Instrument Co., Yellow Springs, Ohio 45387). The technique of SEP monitoring has been described elsewhere for carotid endarterectomy (Russ and Fraedrich, 1984; Russ et al., 1985).

The median nerve was stimulated at the wrist by means of surface electrodes with a constant current of 19.9 mA, a duration of 0.2 ms and a frequency of 3.1 Hz. Recording electrodes were placed above the second spinous process C_2 and above the contralateral cortex C_3', both referred to F_z. The ground electrode was placed near the elbow of the stimulated arm. Two hundred and fifty-six stimuli were averaged with the Nicolet CA 1000 system after amplification (10000) and filtering (30–1500 Hz). The cervical and cortical SEP were recorded simultaneously. Latencies of N14 (N_0), N20 (N_1) and of subsequent cortical peaks (N_2, N_3) were measured, as well as the peak-to-peak amplitudes. Central conduction time (CCT) (the interpeak latency between the primary cortical (N_1) and the cervical SEP (N_0)) was calculated.

In each patient, evoked responses were measured on at least 30 occasions—after the induction of anaesthesia, during the surgical procedure, and during cooling and rewarming on CPB until the patient was transferred to the intensive care unit. Other physiological variables such as arterial pressure and temperature were recorded at the time of SEP analysis.

For statistical evaluation the Kolmogoroff–Smirnow goodness of fit test, variance and covariance techniques for repeated measures were performed. To provide independency of the data, a computer randomly selected, from each patient, the variables from two measurements—one from the first record to the time when cooling was stopped by adjustment of the heat exchanger

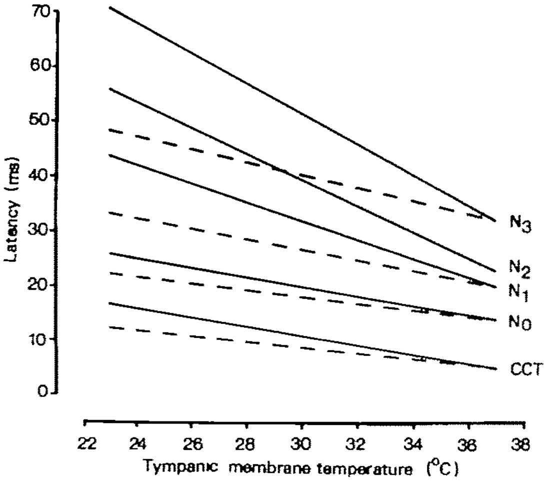

FIG. 1. Regression lines between the cervical peak N_0, different cortical peaks (N_1, N_2, N_3), central conduction time (CCT) and tympanic membrane temperature (t_{ty}) during cooling (——) and rewarming (– – –) on cardiopulmonary bypass (CPB). Slopes of the regression lines increase with peak latencies. The dotted lines represent regression lines during rewarming for CCT, N_0, N_1 and N_3. Note that slopes are different during cooling and rewarming.

TABLE I. *Regression analysis of SEP variables and tympanic membrane temperature during cooling on cardiopulmonary bypass. Slope, intercept and correlation coefficient r are listed for latencies.*
Significance of r is $P < 0.001$

SEP latency (ms)	Slope	Intercept	*r*
N_0	−0.9	45.8	−0.92
P_0	−1.1	58.1	−0.93
N_1	−1.7	82.6	−0.96
P_1	−2.2	103.3	−0.91
N_2	−2.4	110.0	−0.87
P_2	−2.6	120.5	−0.90
N_3	−2.8	134.6	−0.88
P_3	−2.8	154.7	−0.84
CCT	−0.9	36.4	−0.97

(COOLING), the other from the beginning of rewarming to the end of operation (REWARMING). To identify correlations between SEP variables, temperature and perfusion pressure, standard linear regression techniques and non-linear regression techniques (exponential, parabolic) were utilized. $P = 0.01$ was regarded as significant.

RESULTS

The electrical responses of the somatosensory system during hypothermia were very reproducible. As temperature decreased, the latencies of the cervical and cortical SEP increased. The increases were more pronounced for the later cortical peaks N_2 and N_3 than for the specific N_1 and the cervical N_0 (figs 1, 2).

The data fitted best to a linear regression line. Table I summarizes the slopes, intercepts and coefficients of correlation for SEP variables and tympanic membrane temperature during cooling. The best correlation was observed, when tympanic membrane or nasopharyngeal temperatures were used as references (table II).

The amplitudes of the primary cortical SEP showed considerable inter-individual variability, but with the onset of CPB N_1P_1 increased from 2.7 µV to 4.0 µV, and showed a tendency to decrease with decreasing temperature: 15 min after initiation of CPB N_1P_1 was significantly different from the values obtained 3 min after onset of CPB ($P = 0.05$) (table III, fig. 2).

t_{ty} was reduced at a rate of about 0.5 °C min^{-1}, and 15 or 20 min after start of CPB the temperature in the in-line heat exchanger was adjusted to a higher value to establish a steady state temperature. Body temperatures (t_{ty}, t_{np}, t_{rec}) characteristically lagged behind the temperatures of the arterial and venous blood. SEP latencies as well as CCT decreased and N_1P_1 increased instantaneously with increasing blood temperatures, while patients' temperatures were still decreasing (table III, fig. 2). All of the changes described above occurred in reverse order during the rewarming period, with some characteristic differences. From the time when active cooling was stopped (by adjustment of the heat exchanger) to the end of the operation, SEP latencies showed a linear correlation with all temperatures, but the coefficient of correlation was best for the extracorporeal temperatures and worst for rectal

TABLE II. *Correlation coefficient* (r) *between different temperatures and SEP values during cooling and rewarming on CPB. Significance of values: ***$P \leqslant 0.001$; ‡$0.01 \leqslant P \leqslant 0.001$, §$0.05 \leqslant P \leqslant 0.01$; †$P \geqslant 0.05$*

	Cooling					Rewarming				
	t_{np}	t_{ty}	t_{rec}	t_{art}	t_{ven}	t_{np}	t_{ty}	t_{rec}	t_{art}	t_{ven}
CCT	−0.947 ***	−0.974 ***	−0.921 ***	−0.792 ***	−0.882 ***	−0.777 ***	−0.90 ***	−0.56 ‡	−0.95 ***	−0.94 ***
N_1	−0.954 ***	−0.957 ***	−0.883 ***	−0.770 ***	−0.882 ***	−0.856 ***	−0.925 ***	−0 .71 ***	−0.94 ***	−0.957 ***
P_1	−0.926 ***	−0.919 ***	−0.876 ***	−0.841 ***	−0.878 ***	−0.826 ***	−0.78 ***	−0.612 ‡	−0.863 ***	−0.85 ***
N_1P_1	0.275 †	0.172 †	0.263 †	0.505 §	0.529 §	0.494 §	0.248 †	0.311 †	0.29 †	0.344 †
N_0	−0.865 ***	−0.918 ***	−0.812 ***	−0.686 ***	−0.80 ***	−0.772 ***	−0.816 ***	−0.72 ***	−0.825 ***	−0.864 ***
P_0	−0.90 ***	−0.938 ***	−0.870 ***	−0.696 ***	−0.81 ***	−0.843 ***	−0.868 ***	−0.741 ***	−0.858 ***	−0.899 ***
N_0P_0	0.577 ‡	0.444 §	0.325 †	0.4 †	0.367 †	0.096 †	0.2 †	0.22 †	0.248 †	0.22 †

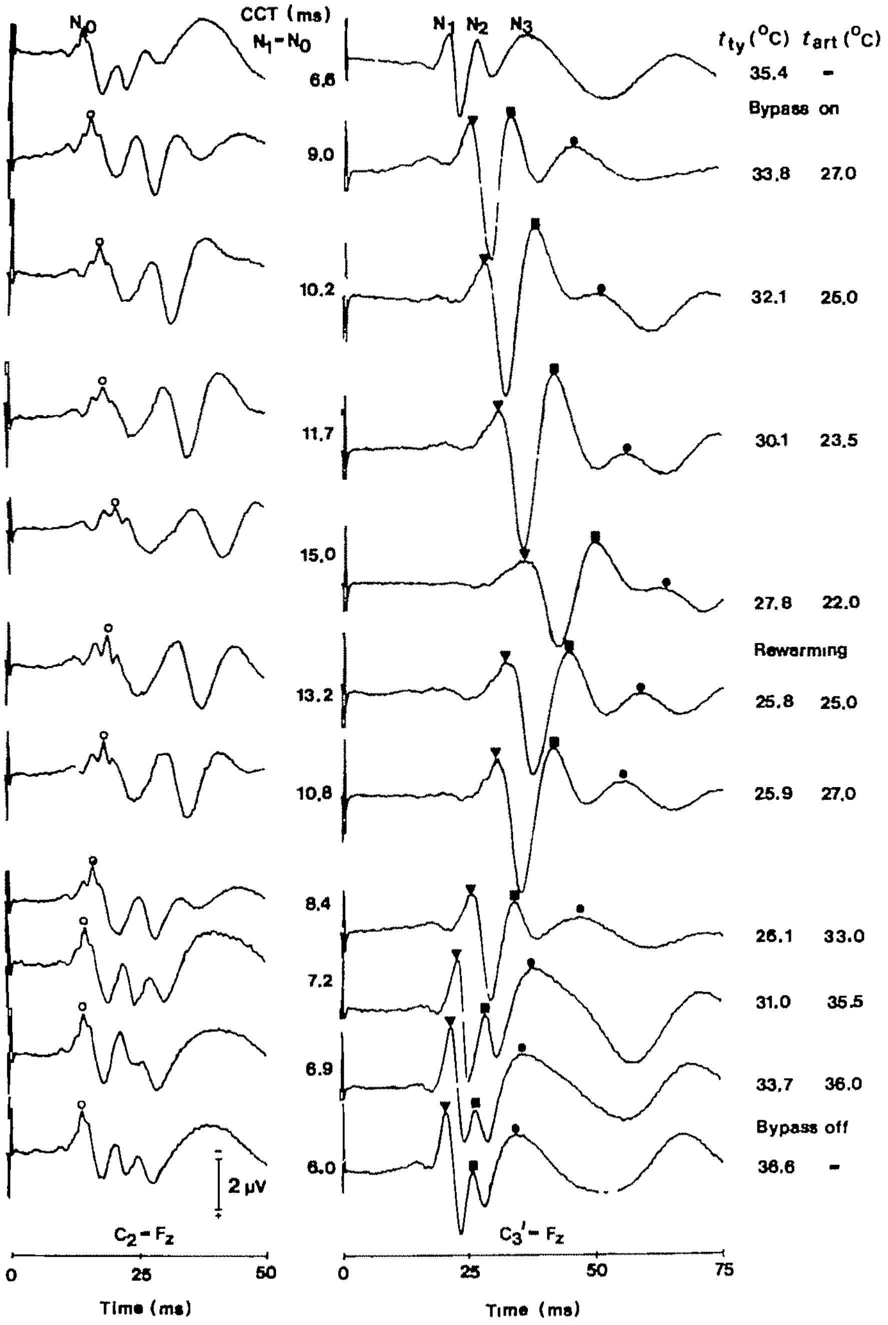

FIG. 2. Somatosensory evoked responses (SEP) after median nerve stimulation in a 53-yr-old man undergoing open heart surgery with cardiopulmonary bypass. Negativity of C_2 or C_3 is presented as an upward deflection. The cervical (N_0) SEP is placed in the left, the cortical (N_1, N_2, N_3) in the right part of the figure. In the upper tracings, after sternotomy, CCT is 6.6 ms and tympanic membrane temperature (t_{ty}) 35.4 °C. With the onset of CPB, CCT and amplitude of N_1 increase. At the end of cooling later cortical peaks (N_3) tend to disappear and the amplitude of N_1 decreases slightly. At the beginning of rewarming, t_{ty} is still decreasing, latencies decrease and amplitudes increase. With increasing temperatures, latencies decrease further and pre-CPB values are achieved at normothermia. t_{ty} lags behind arterial blood temperature during the whole recording period. During hypothermia a splitting of the the cervical SEP into its subcomponents becomes apparent; this phenomenon disappears with normothermia.

TABLE III. *Central conduction time (CCT), amplitude of the primary cortical SEP (N_1P_1), tympanic membrane temperature (t_{ty}) and perfusion pressure immediately before and at intervals after onset of cardiopulmonary bypass. Means ± SD. Significant differences (P ≤ 0.05): *v. pre-CPB; †v. preceding value*

	CCT (ms)	N_1P_1 (μV)	t_{ty} (°C)	Perfusion pressure (mm Hg)
Before bypass	6.6±0.6	2.7±1.2	34.7±0.7	82±17
3 min of CPB	7.0±2.0	4.0±2.3	34.4±0.7	47±15*†
10 min of CPB	10.6±2.0*†	3.0±1.8	31.0±1.6*	58±11*
15 min of CPB	13.5±2.1*	2.1±1.3†	27.6±1.8*	54±11*
20 min of CPB	13.2±2.5*	2.4±1.8	25.8±1.0*	62±19

TABLE IV. *Regression analysis of CCT, N_0 and N_1 and arterial blood temperature during cooling and rewarming on CPB. Slope, intercept and correlation coefficient r are tabulated. Significance of r is P < 0.001*

	Slope	Intercept	*r*
Cooling			
N_0	−0.67	36.2	0.686
N_1	−1.23	60.8	0.771
CCT	−0.56	24.6	0.792
Rewarming			
N_0	−0.59	37.2	0.825
N_1	−1.15	63.6	0.940
CCT	−0.55	26.4	0.950

temperature (table II). The slopes of the regression lines during rewarming were significantly flatter than during cooling (fig. 1) when referred to t_{ty}: CCT increased by 0.85 ms/°C during cooling and decreased by 0.46 ms/°C during rewarming; for the primary cortical negativity N_1 the latency increase was 1.7 ms/°C during cooling and the decrease 0.99 ms/°C during rewarming. Comparable differences were observed for all other latency shifts. When SEP variables were correlated to t_{art} or t_{ven}, nearly identical slopes for the regression lines were observed (table IV).

Institution of CPB resulted in a decrease in mean perfusion pressure from 82 to 44 mm Hg ($P = 0.05$) (table III); later during bypass a trend to higher pressures was observed, with considerable variations. For the entire group no correlation was found between SEP latencies or CCT and perfusion pressure (range 25–110 mm Hg) during cooling or rewarming ($r = 0.1$ and 0.17, respectively ($P = 0.05$)).

At the end of the operative procedure SEP latencies returned to normal at normothermia (fig. 2). The postoperative course of the patients was uneventful and there was no clinical evidence of cerebral impairment.

DISCUSSION

The intraoperative monitoring of somatosensory evoked responses provides a quantitative measure of neural transmission in peripheral and central pathways. N_0 represents the activity of the afferent volley as it ascends the spinal cord and is generated by the dorsal column nuclei. The thalamocortical response to median nerve stimulation is represented by N_1, the specific cortical SEP, which is assumed to originate in Brodman's area 1. N_2 and N_3 represent activities of somatosensory association fields with a widespread hemispheric distribution (Allison et al., 1980; Desmedt and Cheron, 1980).

SEP were selected as a monitor since they have been shown (Branston et al., 1974) to be sensitive indicators of critically reduced regional cerebral blood flow (rCBF). The early component N_1 is topographically specific, and central conduction time (CCT), the interpeak latency between N_1 and N_0, reflects conduction through the lemniscal and thalamic system. Animal studies have shown that the degree of ischaemia necessary to cause disappearance of the EP is less than that necessary for permanent neurological damage (Astrup et al., 1977). This suggests that recognition of alterations in SEP may allow restoration of flow by adequate therapeutic measures before the onset of permanent damage—a concept that has been introduced successfully during carotid reconstructive surgery by means of intraoperative SEP monitoring (Russ and Fraedrich, 1984; Russ et al., 1985). Branston and others (1974) showed that, following middle cerebral artery occlusion in baboons, EP were not affected in areas with an rCBF > 16 ml min^{-1}/100 g; however, when it decreased to less than 12 ml min^{-1}/100 g, EP disappeared; between these two margins SEP amplitude was flow dependent. During hypothermic CPB the effects of temperature on EP have to be considered.

It has been shown in a variety of experimental conditions that, when body temperature is decreased, the electrical output of the system is altered (Brooks, Koizumi and Malcolm, 1955; Cohn and Rosomoff, 1958; Barker and Carpenter, 1970; Weight and Erulkar, 1976). In the present study a progressive diminution in the responsiveness of the somatosensory system was seen and the effects of reduced temperature on peripheral conduction (N_0), central conduction (CCT) and on oligo- and polysynaptic transmission (N_1, N_2, N_3) can be separated. Peripheral and central conduction are delayed to the same extent, expressed by nearly identical slopes for N_0 (−0.87) and CCT (−0.85). The more profound increase in the early cortical N_1 is caused by an additional suppression of synaptic transmission in the lemniscal–thalamic pathway. The later cortical SEP components (N_2, N_3) are slowed to a greater extent since an increasing number of synapses is involved in the generation of these peaks. The physiological principles of these effects were described by Suda, Koizumi and Brooks (1957) and Budnick, McKeown and Wiederholt (1981). Prolonged latencies of potentials from pre-synaptic structures were the result of slowed conduction velocity; potentials from structures with interposed synapses showed a more pronounced delay of latency.

N_2 and N_3 disappeared earlier during cooling, whereas N_0 and N_1 were present in all patients at tympanic membrane temperatures of 26 °C. Mean cortical amplitude was greater than 1.5 µV at this time.

Suda, Koizumi and Brooks (1957) described a diminution of the reflex response in the single afferent fibre of the dorsal column: action potentials from such single units showed an increase in duration and a delayed recovery of normal excitability. Stimulus frequency may, therefore, become an important factor during hypothermia: attenuation of amplitudes increased with stimulus frequency in animal experiments (Budnick, McKeown and Wiederholt, 1981) and during halothane anaesthesia (Gravenstein, Sasse and Hogan, 1984).

One hundred and twenty-eight averages are sufficient to produce a stable waveform, especially when background EEG activity is reduced. A frequency of 2–3 Hz may be the frequency of choice and SEP monitoring can be performed at 1-min intervals. This precludes detection of very short-lived changes. It was found that a phase of hyperresponsiveness did develop after the onset of CPB. This increase in magnitude of the N_1P_1 amplitude became apparent 2–3 min after the initiation of CPB at a temperature of 34.4 °C and persisted until temperature decreased below 31 °C. This increase, however, did not reach statistical significance because of great inter-individual variability in the amplitudes. At the onset of CPB many factors may have an influence on brain electrical activity: flow changes from pulsatile to non-pulsatile, arterial pressure decreases and there is acute haemodilution. The increase in N_1P_1 amplitude is related most probably to the reduction in haematocrit. Comparable results were found by Nagoa, Roccaforte and Moody (1978) during isovolaemic haemodilution. An increase in VEP- and SEP-amplitude was seen when haematocrit was decreased from 40 to 20%.

The independence of perfusion pressure and SEP-variables indicates that the perfusion regimen was safe; a perfusion pressure of 40–50 mm Hg, together with an appropriate flow are tolerated well during hypothermia; Aren and colleagues (1985) reported on somatosensory evoked responses and cerebral metabolism during cardiopulmonary bypass. Although, in a subgroup of patients, perfusion pressure was decreased to 30 mm Hg, alterations in the metabolic demand of the brain and central conduction time were not more compromised than in a control group with a considerably higher perfusion pressure.

Although tympanic membrane temperature is thought to be the best approximation of cranial core temperature (Benzinger, 1969; Davis, Parimelazhagan and Harris, 1977; Ilsley, Rutten and Runciman, 1983; Cork, Vaughan and Humphrey, 1983) this temperature lags behind brain temperature, especially in a system in which temperature changes rapidly with resulting temperature gradients. This was demonstrated at the end of the cooling period: t_{ty} and t_{np} were still decreasing, whereas arterial and venous blood temperatures were increasing. With increasing extracorporeal temperatures, latency decreased instantaneously. The slopes of regression lines for t_{ty} and t_{np} were found to be different during cooling and rewarming. This is probably explained by the assumption that real brain temperature, in the presence of blood–brain temperature gradients, is overestimated during cooling and underestimated during rewarming. Brain temperature is better reflected by t_{art} or t_{ven} in such a dynamic system; slopes for extracorporeal temperatures were found to be nearly identical during the two phases of operation. Comparable phenomena were demonstrated for the effect of hypothermia on visual evoked potentials by Russ and co-workers (1984). Rapid cooling, which implies a great blood–brain temperature gradient, caused more profound alteration in the waveform complexity than moderate temperature reduction. Unfortunately, other groups (Reilly et al., 1978; Coles et al., 1984; Markand et al., 1984; Doyle and Fria, 1985) using rapid cooling with a decrease in temperature of 1 °C min^{-1}, did not analyse these effects separately. It is known from the literature that rapid cooling elicits neural activity, as do gradients between cooled and non-cooled areas (Brooks, Koizumi and Malcolm, 1955; Suda, Koizumi and Brooks, 1957).

Among others, Budnick, McKeown and Wiederholt (1981) and Markand and colleagues (1984) demonstrated that latencies were related to temperature in a linear manner, whereas Coles and co-workers (1984), Doyle and Fria (1985) and Durkin and others (1985), using Arrhenius' transformation of latencies, found that the data fitted an exponential function. In the latter studies the temperature was less than 20 °C, and small infants were investigated. This may in part contribute to the differences.

Our study supports the concepts of a linear correlation in the temperature range 25–35 °C. The insufficient approximation of brain temperature, in the presence of temperature gradients, by t_{ty} or t_{np} should be considered. Exact description of the effects of hypothermia on evoked potential variables require a steady-state temperature (Stockard, Sharbrough and Tinker, 1978)—a situation difficult to achieve under clinical conditions. Therefore, the establishment of different regression lines for cooling and rewarming is necessary or the various indices have to be related to blood temperature.

One limitation of the method presented is that cortical SEP cannot be recorded reliably below 25 °C. In the temperature range 25–35 °C the limitation of SEP monitoring is related to its specificity for the somatosensory afferent and cortical systems. Coles and colleagues (1984) reported on two patients who sustained visual impairment after profound hypothermic circulatory arrest with no alterations in SEP recordings during the operation. Symon, Pasztor and Branston (1974) demonstrated that, after unilateral middle cerebral artery occlusion, the median nerve SEP was not affected, whereas there were marked decreases in the trigeminal nerve cortical potentials. This difference corresponded to appropriate changes in rCBF at the two different sites. A localized reduction of rCBF in other than the stimulated areas, for instance caused by embolism or platelet aggregation, may not be recognized. Reduction of amplitude and increase in CCT were observed when perfusion was reduced to critical values; moderate alterations are probably better represented by computerized EEG techniques.

Malone, Prior and Scholtz (1981) demonstrated that the parieto–occipital region is a sensitive site for the development of minimal lesions, whereas more extensive lesions had a temporal and frontal distribution. Neuropathological findings correlated well with intraoperative cerebral function monitor recordings.

The SEP, along with the BAEP and EEG of the artery boundary zones (Malone, Prior and Scholtz, 1981) could provide the surgeon with sensitive, reliable and rapidly available data concerning brain stem and hemispheric function.

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EFFECTS OF HALOTHANE AND ENFLURANE ON FAR AND NEAR FIELD SOMATOSENSORY EVOKED POTENTIALS

P. S. SEBEL, C. W. ERWIN AND W. K. NEVILLE

SUMMARY

Somatosensory potentials evoked in response to median nerve stimulation were studied in 10 patients during surgery under general anaesthesia with halothane (five patients) or enflurane (five patients). Bipolar scalp responses (near field) and scalp to non-cephalic reference (far field) potentials were recorded before the induction of anaesthesia, and after 15 min stabilization at each of 0.5, 1.0, 1.5 and 2.0% end-tidal concentrations of anaesthetic agent. Both agents produced similar effects. The latency of the bipolar responses was increased and the amplitude decreased. The amplitude of the far field, subcortically generated, potentials measured from the scalp to non-cephalic electrodes did not decrease as much as the near field potential with increasing concentrations of volatile anaesthetic, although the latency of the potential recorded at the frontal electrode increased. At higher anaesthetic concentrations the virtual elimination of the near field potential caused the frontal and rolandic potentials to appear to be identical. Since far field somatosensory evoked potentials are preserved during deep anaesthesia, they should be considered for use when measurement of evoked responses is required for monitoring purposes.

Intraoperative monitoring of sensory evoked potentials is used to test the integrity of specific neural pathways during surgery (Grundy, 1983) and to characterize the effects of anaesthetic agents (Sebel, Heneghan and Ingram, 1985). Anaesthetic agents affect cortically generated potentials markedly, often rendering them unrecordable (Grundy, 1983; Thornton et al., 1984; Sebel et al., 1986). Subcortically generated potentials, such as the brain stem auditory evoked potential (BAEP), are less affected by anaesthetic agents than are the cortically generated potentials (Grundy, 1983; Thornton et al., 1984). When somatosensory evoked potential (SEP) monitoring is used during anaesthesia, a bipolar derivation is commonly used (Grundy, 1983; Sebel et al., 1986). This represents the potential difference recorded between electrodes placed over the somatosensory cortex and another electrode, usually frontal in position.

The concepts of near field and far field generators of evoked potentials provide a basis by which the effects of anaesthetics on evoked potentials may be better understood. Far field scalp potentials are usually generated in subcortical structures, an example being the BAEP. The potentials reach the scalp electrodes by volume conduction through electrolyte-rich fluids rather than through neural pathways. The voltage field distribution is very broad. Thus, far field evoked potentials are usually low in amplitude, early in latency, and have a non-specific, broad topography. This latter factor causes far field activity to cancel in derivations using electrodes within the field. A non-cephalic reference electrode (NCR) may be required to "reveal" the activity. In contrast, near field activity is generated at the cortex, after arrival through neural pathways and is later, larger and more specific in topography (Erwin et al., 1986).

Confusion arises when near field and far field events occur at the same time. This is the case with the median nerve somatosensory response. Beginning approximately 18 ms after stimulation

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P. S. SEBEL, M.B., B.S., PH.D., F.F.A.R.C.S.I., Anaesthetic Unit, The London Hospital Medical College, Whitechapel, London E1 1BB. C. W. ERWIN, M.D.; W. K. NEVILLE, B.A.; Evoked Potential Laboratory, Duke University Medical Center, P.O. Box 3094, Durham, N.C. 27710, U.S.A. Accepted for Publication: April 27, 1987.

at the wrist, a broadly distributed negative wave, called the N18 by Desmedt and Cheron (1981), is recorded bilaterally. Superimposed on this wave is the cortically generated near field component, usually called the N20 (Guidelines, 1984). The far field N18 can only be recorded with a derivation including an NCR electrode. In this paper the N18 is called "far field" and "subcortical". In bipolar derivations, the N18 is suppressed by common mode rejection, leaving the near field N20 uncontaminated. In this paper the N20 is called the "bipolar cortical response" and "near field."

This study was designed to investigate the effects of halothane and enflurane on far field SEP.

PATIENTS AND METHODS

After institutional review board approval, 10 female patients (age 38.7±8.9 yr, weight 61.6±11.3 kg), scheduled to undergo elective gynaecological surgery expected to last more than 60 min, gave informed consent to the study. SEP recordings were made using a Cadwell 7400. The low-cut filter was set at 10 Hz, the high-cut filter at 1000 Hz and the averager epoch was 50 ms. Adhesive electrodes (Meditronic TENS electrodes) were placed over the median nerve, which was stimulated with a constant-current pulse generator set at 150% of motor threshold at a rate of 10 Hz for 800 repetitions. The SEP were recorded using silver–silver chloride electrodes in the following derivations, based on the international 10–20 system (Jasper, 1958):

(1) C_5S–F_{pz} (5th cervical vertebra–frontal)

(2) C_3'–F_{pz} (C_3' is a rolandic placement midway between C_3 and P_3).

(3) C_3'–shoulder (C_3' to shoulder contralateral to stimulation).

(4) F_{pz}–shoulder (frontal–shoulder contralateral to stimulation).

Electrode resistances were less than 2 kΩ in all cases. All SEP were in duplicate. After premedication with diazepam 10 mg, baseline recordings were obtained. Anaesthesia was induced with a "sleep" dose of thiopentone; pancuronium was used to facilitate tracheal intubation and the lungs were ventilated with nitrous oxide in oxygen

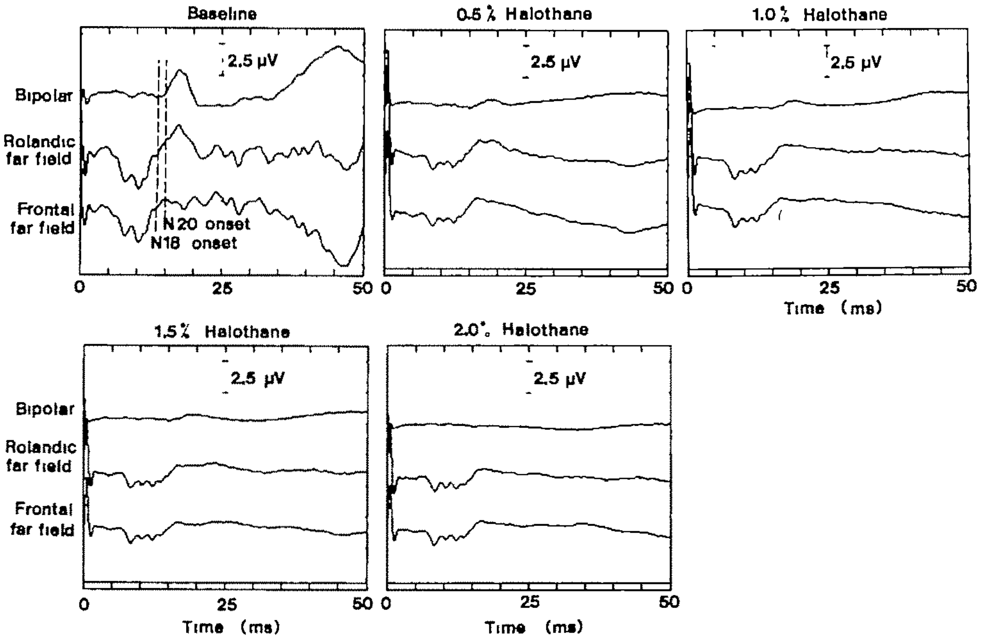

FIG. 1. Sequence of changes in evoked potentials in one subject during halothane administration. The baseline recording, on which the onset of the N18 and N20 are shown, was taken before induction of anaesthesia. With increasing concentrations of halothane, a progressive reduction in amplitude and increase in latency of the bipolar recording is seen. With 0.5% halothane, a small difference between the two far field derivations can be seen, but at concentrations higher than that, the far field potentials are identical.

($F\text{I}_{O_2} = 0.4$). Enflurane or halothane was then introduced and the end-tidal concentration, measured with a Puritan–Bennett anaesthetic agent monitor, was adjusted to 2%. This device measures anaesthetic agent concentration by infra-red absorption and is insensitive to water vapour. The maximum response time is 600 ms. This concentration was maintained for 15 min, after which SEP were recorded.

The concentration of volatile agent was then decreased in decrements of 0.5% until a concentration of 0.5% was reached. If time allowed, the concentration was then increased stepwise. At the end of each 15-min period, SEP were recorded. The latency of the SEP was measured from the time of stimulus to the first major negative (upward deflection) peak. For the cortical, near field SEP, measurements of amplitude were made from the negative peak to the next positive valley. For the rolandic (C_3') and frontal (F_{pz}) far field potentials, there was generally no obvious succeeding positive valley (fig. 1). Therefore, measurements of amplitude on the far field potentials were made from the positive trough occurring at approximately 13 ms (N13) to the greatest negative peak. Statistical analysis was with repeated measures analysis of variance (BMDP2V (Dixon, 1985)).

RESULTS

Halothane and enflurane appeared to produce the same effects on SEP. The recordings from over the 5th cervical vertebra did not alter significantly during anaesthesia, nor did the N13 peak in the far field potentials, and these are not considered further.

Figure 1 shows a typical sequence of recordings from one subject during halothane anaesthesia. In the example shown, the bipolar, cortical SEP increases in latency and decreases in amplitude with increasing concentrations of halothane, becoming unmeasurable at 2.0% end-expired halothane concentration. After the administration of halothane, the two far field potentials become morphologically similar. At 0.5 and 1.0% halothane, some small differences can be seen between the two different electrode derivations, but at concentrations greater than 1% the far field potentials become identical. There are no marked increases in latency of the far field potentials, although the amplitude of both derivations is attenuated with halothane.

The evoked potential variables for the two groups of patients are shown in table I. The alterations seen on decreasing anaesthetic concentration were the same as seen when the

TABLE I. *Evoked potential variables (mean ± SD) during halothane (five patients) or enflurane (five patients)*

	Bipolar		Rolandic far field		Frontal far field	
	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)	Latency (ms)	Amplitude (μV)
Halothane						
Baseline	18.8±0.3	2.8±2.7	17.9±0.5	3.8±2.2	17.3±0.4	2.9±1.2
0.5%	20.1±0.9	0.7±0.2	18.8±1.0	2.6±0.6	18.3±0.9	2.1±0.6
1.0%	19.9±1.4	0.6±0.1	18.5±0.8	2.6±0.6	18.3±0.8	2.4±0.5
1.5%	20.2±1.8	0.4±0.1	18.5±0.9	2.2±0.3	18.4±0.7	2.0±0.4
2.0%	20.4±1.4	0.3±0.1	18.8±1.3	2.0±0.6	18.5±1.1	1.8±0.6
F	1.82	2.19	1.31	1.06	3.18	1.42
P	0.22	0.16	0.34	0.43	0.07	0.31
Enflurane						
Baseline	18.1±0.9	2.7±0.0	18.1±0.8	3.6±1.3	16.9±2.6	2.5±0.8
0.5%	20.0±1.5	0.5±0.1	19.4±2.5	2.5±0.5	18.6±3.0	1.9±0.1
1.0%	20.2±1.6	0.6±0.1	19.7±2.2	2.1±0.2	18.7±2.7	1.8±0.1
1.5%	20.2±1.1	0.6±0.0	18.8±2.8	2.2±0.5	18.5±2.4	1.9±0.4
2.0%	19.8±1.2	0.5±0.1	19.0±3.0	1.7±0.2	19.0±2.8	1.7±0.1
F	24.2	338.2	0.98	1.81	33.93	0.88
P	0.00	0.00	0.50	0.29	0.00	0.54

concentration was increased and mean values are reported at each anaesthetic concentration. Enflurane anaesthesia was associated with a statistically significant increase in bipolar evoked potential latency and a decrease in amplitude. The changes seen with halothane were similar in degree, but did not reach statistical significance. There was a large standard deviation in the baseline measurements in the halothane group as a result of one patient who had a baseline amplitude of 6 μV on repeated testing. The only statistically significant changes in far field potentials were an increase in latency of the frontal far field potential seen with halothane and enflurane.

DISCUSSION

The monitoring of evoked responses is used commonly to assess the integrity of specific neural tracts during anaesthesia (Grundy, 1983). When undertaking such monitoring, it is important to be aware of the effects of anaesthesia on the potentials being recorded and to make allowances for these. It has been suggested that monitoring cortical evoked potentials may provide a neurophysiological index of depth of anaesthesia (Sebel, Heneghan and Ingram, 1985), although it is unclear whether the somatosensory (Sebel et al., 1986) or the early cortical components of the auditory response (Jones and Konieczko, 1986) will be the more useful.

To date, there have been limited studies of the effects of anaesthesia on subcortically generated evoked responses. The only response that has been studied in any detail is the brain stem auditory evoked responses (that is, the first 10 ms of the auditory evoked response). This response is resistant to the effects of anaesthesia. Very small increments in the latencies of the various components of the brain stem response occur with volatile agents (Thornton et al., 1984; Sebel et al., 1986), but the i.v. anaesthetics and nitrous oxide do not affect this response (Sebel, Flynn and Ingram, 1984; Thornton et al., 1985).

The findings of the present study confirm previously described relationships for the volatile anaesthetic agents, particularly with regard to decreases in the amplitude of the cortical bipolar response (Thornton et al., 1984; Sebel et al., 1986). The alterations in the far field potentials can be attributed in a major part to the "fall out" of the cortical components from the cortical far field potential. As the cortical bipolar response becomes smaller, the morphology of the cortical and frontal far field potentials becomes similar. The generator site for the far field N18 potential is uncertain, but probably reflects subcortical activities such as delayed or reverberating potentials in the mesencephalic reticular system, the thalamus itself, or action potentials in the lower part of the thalmocortical axons. The near field N20 is thought to represent the earlier ("primary") cortical response in the projection areas 3-1-2 of somatosensory cortex (Desmedt and Cheron, 1981; Tsuji et al., 1984).

It has been suggested that satisfactory cortical SEP can be recorded during halothane anaesthesia for spinal fusion procedures (Salzman et al., 1986). However, that study was poorly controlled because the administration of halothane was not standardized and no measurements of halothane concentration were made. In 78 of their patients, only 0.5 % halothane was used. Halothane concentrations greater than 0.75 % decreased the incidence of successful monitoring of SEP. Our data suggest that when deep halothane (> 1.0 % end-tidal expired) anaesthesia is used, and evoked potential monitoring is required, it is difficult if not impossible to monitor the bipolar cortical derivation and more useful to monitor subcortical potentials. However, the bipolar cortical potentials are more appropriate for monitoring anaesthetic effects on those central nervous system functions related to depth of anaesthesia.

It is surprising that anaesthetic agents exert different effects on cortical and subcortical potentials. Assuming that volatile anaesthetics act by depressing neuronal function, increases in latency and decreases in amplitude of evoked potentials can be explained on the basis that the rate of neuronal transmission and the number of neurones firing are decreased. It is unclear why a similar effect is not seen in far field subcortically genererated potentials and in spinal evoked potentials. There are fewer intervening synapses involved in the generation of the subcortical potentials than of cortical potentials. The greater number of synapses involved in generation of the cortical potentials may explain why they are more affected by anaesthetic agents.

In previous studies (Sebel, Flynn and Ingram, 1984; Sebel et al., 1986) we have used relatively slow rates of median nerve stimulation (2 Hz). The optimal rate for stimulation of the median nerve during general anaesthesia has yet to be determined. The amplitude of the evoked response will decrease as the rate of stimulation is increased, but rates of up to 20 Hz do not attenuate peak amplitude (Erwin, Brendle and Solomon, 1985). Unfortunately, stimulation at this rate is painful in the awake subject. In order to obtain good quality recordings, we wanted to use the largest number of averages possible within a reasonable time period. Since patients will tolerate stimulation at 10 Hz we chose to use this rate for 800 repetitions.

Previous studies by ourselves and others have shown that anaesthetic agents, both volatile and i.v., exert a graded effect on cortical evoked potentials (Thornton et al., 1984; Sebel, Heneghan and Ingram, 1985; Thornton et al., 1985). The results from the present study are at variance with these observations, for we observed a marked decrease in amplitude with an increase in latency at end-tidal concentrations of 0.5% halothane or enflurane compared with the awake potentials. However, there was a further effect of increasing anaesthetic agent concentration about 0.5%. There were no differences between enflurane and halothane at the same concentrations, although the two have different potencies. It is possible that these findings were a result of the increased stimulation rate used compared with previous studies. The higher rate may have produced some amplitude attenuation, such that a graded response could not be discerned (note that the amplitude measurements were approximately 0.5 μV during anaesthesia in this study). Formal studies of the optimal rate for posterior tibial nerve stimulation have been carried out (Nuwer and Dawson, 1984), but they are lacking for median nerve stimulation. It is possible that the higher the rate of stimulation, the less sensitive the response to anaesthetic effects. The hypothesis requires testing.

In conclusion, we have shown that far field SEP can be reliably recorded during deep halothane and enflurane anaesthesia. Monitoring of these potentials should be considered when preservation of evoked responses is required.

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SOME VENTILATORY EFFECTS OF PROPOFOL AS SOLE ANAESTHETIC AGENT

N. W. GOODMAN, A. M. S. BLACK AND J. A. CARTER

Di-isopropyl phenol is metabolized rapidly and should be a good anaesthetic agent to give by continuous i.v. infusion (Cockshott, 1985). The aim of our study was to measure resting ventilation, and the response to carbon dioxide, in patients anaesthetized with propofol alone, and in the absence of surgical stimulation. Since it was not feasible to prolong the period of anaesthesia before surgery, a subarachnoid anaesthetic was given to patients scheduled to undergo surgery to the lower limbs. The patients were then studied during surgery. We obtained approval from the local ethics committee. A preliminary report has been published (Goodman, Carter and Black, 1985).

PATIENTS AND METHODS

Patients, preparation and plan

We approached 30 suitable patients of ASA grade I, aged between 18 and 65 yr; 16 gave informed consent: 10 males and six females, aged between 22 and 64 yr and weighing between 53 and 96 kg, were included in the study.

The patients were unpremedicated. Two i.v. cannulae were sited in the non-dominant arm: a 17-gauge cannula for the infusion of Hartmann's solution and an 18-gauge cannula for injection and infusion of propofol (1% in 10% emulsion). Subarachnoid anaesthesia was effected by heavy 0.5% cinchocaine 1.4–1.6 ml or heavy 0.5% bupavacaine 3–3.5 ml using a 26-gauge needle. Arterial pressure was measured using an automatic device (Critikon: Dinamap 845) with the cuff on the dominant arm.

Once the subarachnoid anaesthesia was effective, the patients breathed 100% oxygen by face mask until the end-tidal carbon dioxide ($P\text{E}'_{CO_2}$) was stable. Pre-induction ventilation and $P\text{E}'_{CO_2}$ were recorded for 1 min before anaesthesia was

SUMMARY

Ventilatory effects of propofol, used as a sole agent for the induction and maintenance of general anaesthesia, were studied in 14 healthy unpremedicated patients. Subarachnoid anaesthesia was established before induction of general anaesthesia. Induction was with propofol 2.5 mg kg^{-1} given while the patients breathed 100% oxygen. We intended to start an infusion of propofol 100 µg kg^{-1} min^{-1}; maintain it for at least 25 min; make a first set of quasi-steady-state observations; double the infusion; and repeat observations after 25 min. The single induction bolus plus single rate infusion was not totally satisfactory: further boluses were usually needed. At induction there was apnoea in all but three patients, sometimes lasting more than 3 min; hyperventilation before induction, combined with hyperoxia, probably exaggerated this. Established ventilatory rates were generally 30% higher than awake. One patient became bradypnoeic. Tidal volume and minute ventilation, and the $T_I:T^{tot}$ ratio, were reduced. Doubling the infusion rate had no clear effect on frequency or tidal volume, but it further reduced the $T_I:T^{tot}$ ratio and caused an increase in $P\text{E}'_{CO_2}$ of 1 kPa. The ventilatory response to carbon dioxide was 58% of baseline awake control (95% confidence limits ±26%) at the lower infusion rate, with further slight depression when the infusion rate was doubled. Doubling the rate of infusion of propofol did not give twice the effect on ventilation, and probably is not giving twice the "depth" of anaesthesia. We cannot say if this is for pharmacokinetic or pharmacodynamic reasons.

N. W. GOODMAN, M.A., D.PHIL., F.F.A.R.C.S.; A. M. S. BLACK, M.A., D.PHIL., F.F.A.R.C.S.; J. A. CARTER, F.F.A.R.C.S.; University Department of Anaesthesia, Southmead Hospital, Bristol BS10 5NB. Accepted for Publication: July 31, 1987.

induced with propofol 2.5 mg kg^{-1} over about 30 s, and an infusion at a rate of 100 µg kg^{-1} min^{-1} (6 mg kg^{-1} h^{-1}) via a syringe pump (Dylade Injectomat 50) was started. Ventilatory recordings were continued during induction and for the following 3 min, after which the patients were moved into the operating theatre and settled on the table. During this period all but two of the patients needed at least one supplement of propofol (40–50 mg), because of signs of arousal.

Our plan, thereafter, was to wait at least 25 min at the initial infusion rate, record resting ventilation and the ventilatory response to carbon dioxide, then double the infusion rate and repeat the ventilatory measurements after a further 25 min. If there was still operating time in hand, we planned to repeat ventilatory measurements at the higher or lower infusion rate as convenient.

Our adherence to this plan depended partly on the adequacy of the anaesthesia and partly on the duration of the surgery and we completed satisfactory observations at both infusion rates in only seven of the 16 patients who agreed to participate. Three others were studied only at the lower infusion rate (because operations were shorter than expected); four were studied only at the higher rate (because of inadequate anaesthesia at the lower rate); and two were too unsettled, even at the higher rate, to give a complete set of satisfactory ventilatory measurements.

We obtained conscious baseline carbon dioxide responses from eight patients, either before they left hospital or at their convenience after discharge. Six of these patients had been studied at both infusion rates, and two at the lower infusion rate only.

Ventilatory measurements

We modified a conventional circle breathing system, replacing the normal 2-litre bag by two interconnecting bags. A tap allowed use of one or other bag, or of both. One bag of volume 6 litre was contained in a Perspex bottle (bag-in-bottle), and the other, of 4 litre, was outside the bottle. The bag-in-bottle was used when measuring ventilation: the movements of the bag displaced air from the bottle through a Fleisch head, and the signal of flow was then integrated (Godart pneumotachograph type 17212). The outside bag was used to supply gas to the patient while the bag-in-bottle was being filled.

The patient breathed from a face mask held carefully to the face so as to avoid leakage or entrainment. Carbon dioxide was measured continuously (Gould Godart capnograph Mark III), taking gas via an Engstrom "Aridus" sampling tube from the angle piece at the mask and returning it to the expiratory limb of the circuit. An "Oxycheck" polarographic oxygen analyser was used to measure the oxygen concentration of the gas in the inspiratory limb.

For measuring unstimulated ventilation, the patient breathed 100% oxygen from the bag-in-bottle with the carbon dioxide absorber switched into the circuit. For the ventilatory response to carbon dioxide we used the Read rebreathing technique (Read, 1967). While the patient breathed 100% oxygen from the outside bag, we filled the bag-in-bottle with carbon dioxide in oxygen to a carbon dioxide concentration at least 1% higher than the patient's measured end-tidal carbon dioxide. The bag was filled until it was slightly distended. To start the rebreathing manoeuvre, we switched the carbon dioxide absorber out of circuit and switched from the outside bag to the bag-in-bottle. The excess gas in the bag-in-bottle flushed the carbon dioxide-free gas out of the circuit through a spill valve which was then screwed down. Switching during expiration ensured that the next inspiration consisted of the carbon dioxide-enriched gas. Signals representing ventilation and $P\text{E}'_{\text{CO}_2}$ passed to a two-channel pen recorder (paper speed 25 mm min^{-1}) and to an Apple IIe microcomputer for storage and analysis of the ventilatory response to carbon dioxide which was generally based on least squares linear regression using breath-by-breath data (Goodman and Curnow, 1985). The analysis used (Rebuck, 1976) only that part of the response, after the first 30 s or so, in which the inspired was close to the expired carbon dioxide concentration and the expired carbon dioxide concentration was increasing linearly with time, as judged by eye.

For the conscious rebreathing responses, we performed at least three tests. The first was always rejected as a practice; it was sometimes necessary to reject others for technical reasons. We rarely had to reject, for technical reasons, responses from the anaesthetized patients.

RESULTS

Tidal volume, frequency and minute ventilation

The upper two blocks of table I are a summary of the changes in these ventilatory variables in the 14 patients that we were able to study at one or

TABLE I. *Tidal volume* (V_T), *ventilatory frequency* (f), *minute ventilation* ($\dot{V}_I$), *and inspiratory duty cycle* ($T_I:T^{tot}$) (*mean values and range*) *before and after induction and on the two infusion rates of propofol. Upper block: values for the seven patients studied at all stages. Middle block: overall values for the 14 patients. Lower block: comparisons of* $T_I:T^{tot}$ *in six patients at all stages. Post-induction measurements were made in the first 1 min of measurable ventilation after induction; values for* V_T *and* $\dot{V}_I$ *are meaningless because* V_T *was usually steadily increasing over this time* ($T_I:T^{tot}$ *not measured*)

	Pre-induction	Post-induction	Low infusion	High infusion
No. patients	7	7	7	7
V_T (ml)	700(375–1145)	—	455(300–520)	380(290–505)
f (b.p.m.)	11.8(8.9–16.1)	15.8(11.7–21)	14.4(11.7–17.2)	14.1(8.7–18.0)
$\dot{V}_I$ (litre min^{-1})	7.8(3.7–13.2)	—	6.5(4.1–8.1)	5.4 (3.3–7.3)
No. patients	14	14	10	11
V_T (ml)	725(380–1140)	—	470(300–520)	420(290–690)
f (b.p.m.)	11.7(4.9–16.1)	17.8(9.7–25)	14.2(7.7–19.4)	16.1(8.7–27.2)
$\dot{V}_I$ (litre min^{-1})	8.0(3.17–13.2)	—	6.5(4.1–8.5)	6.8(3.3–18.8)
No. patients	6	6	6	6
$T_I:T^{tot}$	0.46(0.42–0.50)	—	0.40(0.34–0.45)	0.34(0.26–0.40)

other infusion rate. The upper block presents data from the seven patients studied at both infusion rates; the middle block presents all the available data at both infusion rates.

Pre-induction. All patients were affected to some extent by anxiety and unfamiliarity: two had a minute ventilation ($\dot{V}_I$) of 13 litre min^{-1} and one of these had a $P_{E'CO_2}$ of 2.5 kPa; the others were less extreme.

Post-induction. The ventilatory reaction to the induction of anaesthesia with propofol was varied, but common features were: a profound initial reduction in tidal volume, an early and marked tachypnoea, and a decrease in the inspiratory duty cycle ($T_I:T^{tot}$ ratio). As with other i.v. induction agents, the "moment" of induction was often marked by a sigh or yawn about 20–30 s after the start of the injection. The reduction in tidal volume was usually maximal within 30 s of the start of the effect and progressed to a period of apnoea which lasted between 30 s and 5 min in 11 of the 14 patients. Patients' lungs were ventilated gently by hand with 100% oxygen if the patient was apnoeic for more than about 1 min. After the period of apnoea, breathing resumed with small tidal volumes which increased over 1 min or so to a fairly steady post-induction value. This increase was often incomplete by the time the patient moved enough to receive a supplementary dose of propofol.

Most patients showed an increase in ventilatory frequency. In two patients, in whom the tidal volume remained discernible throughout the period of gross reduction of ventilation, tachypnoea became evident immediately, and persisted. In those patients who became apnoeic this tachypnoea was evident as soon as tidal volumes became discernible again. The rate, once ventilation was re-established, was regular, with no grossly irregular or periodic breathing.

Three patients showed a small reduction in ventilatory frequency after induction; one of these patients was particularly anxious and had the highest recorded pre-induction frequency of 16.1 b.p.m. In one exceptional patient, whose tidal volume, although very low, was discernible throughout induction, the ventilatory rate decreased sharply from a pre-induction value of 15 to 9.7 b.p.m.

During infusion. The post-induction tachypnoea tended to stabilize as anaesthesia was maintained. The rate of ventilation in the patient who had shown the abrupt slowing on induction, slowed further to 7.7 b.p.m. In four patients the frequency increased further after the induction period, and in one of these, whose ventilatory rate reached 27.2 b.p.m., we had later to abandon the infusion technique after making our ventilatory measurements.

The mean values for the seven patients studied at both infusion rates (table I, upper block) indicate a decrease in V_T and an increase in frequency between consciousness and on infusion at the lower rate. V_T was further reduced with little change in frequency on going from the low to the high infusion rate. The changes in V_T and frequency between consciousness and the high infusion rate were significant even in this small sample ($P < 0.05$, Wilcoxon test for pair differences); the pattern shown in the upper block of table I is supported by the fuller data on all 14 patients, presented in the middle block of table I.

The net effect of the changes in tidal volume and rate over this period was that $\dot{V}\text{I}$ did not change in any consistent direction from pre-induction values, and any changes were small, unless pre-induction $\dot{V}\text{I}$ was high. $\dot{V}\text{I}$ was always lower if pre-induction $\dot{V}\text{I}$ had been greater than 8 litre min^{-1}.

Inspiratory duty cycle

The paper tracing of ventilatory volume from all patients showed a decrease of $T\text{I}:T^{\text{tot}}$ at the moment of induction. Table I, lower block, shows the mean ratios for six of the seven patients studied at both infusion rates. The data during induction were not collected by computer from the seventh patient. The overall decreases from awake to low to high infusion rates were seen consistently in every patient, and were reversed in the two patients who were later returned from the high to the low infusion rate.

End-tidal carbon dioxide

In three patients the $P\text{E}'_{\text{CO}_2}$ was less than 4 kPa at induction; the highest was 5.6 kPa. It was apparent that, in some patients, particularly those with low tidal volumes, $P\text{E}'_{\text{CO}_2}$ did not reach a convincing plateau and thus could not reflect alveolar partial pressures during anaesthesia, probably because of series deadspace effects. The highest $P\text{E}'_{\text{CO}_2}$ recorded during low infusions was 6.1 kPa, and during high infusions 7.4 kPa (56 mm Hg). In all seven patients studied at both infusion rates, $P\text{E}'_{\text{CO}_2}$ was always higher at the higher infusion ($P < 0.01$, Wilcoxon test for pair differences).

Ventilatory responses to carbon dioxide

Table II shows the gradient obtained, arranged so that gradients from each condition (awake, low, high) form unbroken columns. Standard errors for individual gradients (not tabulated) were generally between 10% and 20% of the gradient, and correspond to statistical confidence limits on the individual gradients of about 20–40%.

In the eight patients who were studied both awake and under anaesthesia, carbon dioxide sensitivity was significantly less under anaesthesia with the low infusion than in the awake state ($P < 0.025$, Wilcoxon test for pair differences). Six of the seven patients who were tested at both infusions showed further small reductions in carbon dioxide sensitivity. For subject 9, the sensitivity remained greater than that recorded when awake.

TABLE II. *Sensitivity to carbon dioxide by rebreathing (litre* $\textit{min}^{-1}\ \textit{kPa}^{-1}$*): awake, during low (100-μg* $\textit{kg}^{-1}\ \textit{min}^{-1}$*), and high (200-μg* $\textit{kg}^{-1}\ \textit{min}^{-1}$*) infusions of propofol. (2)Figure is an average of two tests. *Significant difference by the Wilcoxon test for pair differences*

Subject	Slope of CO_2 rebreathing manoeuvre (litre $\text{min}^{-1}\ \text{kPa}^{-1}$) Awake	Low infusion	High infusion
2	—	—	7.8
4	—	—	2.7
6	—	—	2.9
11	—	—	8.3
12	—	2.7	2.3
7	16.4(2)	6.6(2)	4.1(2)
8	16.2(2)	5.5	5.1
9	11.1	12.8	11.6
10	15.4(2)	12.7	10.9
13	17.6(2)	5.9(2)	9.1
16	5.4(2)	4.4	2.8
14	15.5	6.9	—
15	11.5	3.7	—
5	—	3.4	—
Overall means	13.6	6.5	6.1
Paired means	13.7*	7.3*	
		7.2	6.5

We carried out repeat measurements of carbon dioxide responses under anaesthesia, which enabled us to verify the consistency of the responses, in two patients: patient 7 gave carbon dioxide sensitivities of 7.7 then 5.5 litre $\text{min}^{-1}\ \text{kPa}^{-1}$ at the low infusion rate, 2.9 then 5.2 litre $\text{min}^{-1}\ \text{kPa}^{-1}$ at the high rate; subject 13 gave 5.9 litre $\text{min}^{-1}\ \text{kPa}^{-1}$ at the low rate, 9.1 litre $\text{min}^{-1}\ \text{kPa}^{-1}$ at the high rate, and then 5.8 litre $\text{min}^{-1}\ \text{kPa}^{-1}$ when returned again to the lower rate.

The mean intercept on the $P\text{E}'_{\text{CO}_2}$ axis was 5.5 kPa when awake, 4.9 kPa during the low infusion, and 5.3 kPa during the high infusion. There was a significant difference ($P < 0.025$, Wilcoxon test for pair differences) between the intercepts at the two infusion rates, but not between the intercepts from the awake state and at the lower infusion.

DISCUSSION

Study design

We intended to investigate the ventilatory effects of propofol, uncomplicated by premedicant or other anaesthetic drugs, and in the absence of surgical stimulation. It is clear now that the results do not necessarily reflect the pure effects of propofol. The clinical situation was not quite normal and the subjects may not have been normal or, if they were, may not have been in their normal state of mind.

We had difficulty in recruiting patients to the study: the acceptance rate was just over 50% (Goodman and Black, 1986). The refusals were partly because of anxieties about a new drug, and partly because of worries about undergoing subarachnoid anaesthesia. Those who did accept may have been from a particularly stoical or easy-going subgroup of the general population. Even so, most patients came to the anaesthetic room anxious; most were hyperventilating before induction and the resulting hypocapnoea, coupled with the oxygen breathing, probably exaggerated the incidence and duration of post-induction apnoea and hypoventilation.

We did not include awake, baseline responses to carbon dioxide as an essential part of the study design because of the shortage of time in the preoperative period, our own published experience (Goodman and Black, 1985), and the experience of others who have used the Read rebreathing technique in awake untrained subjects (Jordan, 1982). Fortunately, eight patients were able to return, either before or after their discharge from hospital, to provide something closer to "normal" estimates of awake ventilatory pattern and sensitivity to carbon dioxide, without the pressures of a preoperative timetable and preoperative anxieties.

The spinal anaesthesia, intended to remove the disturbing effects of surgical stimulation, clearly could not obtund the stimulus caused by holding on the face mask and maintaining the airway under anaesthesia. Spinal anaesthesia may also have introduced disturbances of its own, but we cannot say whether these affected our measurements.

Quality of anaesthesia

Our induction dose of 2.5 mg kg^{-1} was probably greater than necessary (Redfern, Stafford and Hull, 1985; Bilaine and Desmonts, 1985; Rolly, Versichelen and Herregods, 1985), and was probably another contributory factor in the incidence of hypoventilation and apnoea. Hypotension was not a striking feature in our study, perhaps because the vasomotor tone was already reduced by the spinal anaesthesia and the expanded vascular capacity was already somewhat filled before the induction of general anaesthesia.

We chose 100 μg kg^{-1} min^{-1} as our baseline infusion rate of propofol expecting to be able to anaesthetize most of our patients, and doubling it was intended to be supra-effective. This was based on a figure for the infusion ED$_{50}$ of between 50 and 60 μg kg^{-1} min^{-1}, after morphine premedication and with patients breathing 67% nitrous oxide in oxygen (Coates et al., 1985). Mackenzie and Grant (1985) used a mean dose of 130 μg kg^{-1} min^{-1}, though as intermittent boluses, under conditions similar to ours. Jessop and coworkers (1985) used a mean of 103 μg kg^{-1} min^{-1} as an infusion to premedicated patients. It is not surprising that some of our patients would not settle at the lower rate, but we were disappointed that three out of 16 would not settle even at the higher rate. We are confident that surgical stimulation played no part in this because the operated area was still anaesthetic at recovery in all patients.

Movement in response to surgical stimulation is the criterion for estimating MAC for an inhalation agent. In our study it became clear that movement was not necessarily an indication of inadequate anaesthesia; the patient who took longest to wake showed spontaneous movements throughout. Another difficulty was that patients established on an infusion rate at a stable $P\text{E}'_{CO_2}$ could show signs of arousal during rebreathing.

Others have reported good recovery after propofol in more formal studies of recovery (Grant and Mackenzie, 1985) and we certainly felt that the striking feature about propofol as an infusion anaesthetic was the rapidity with which cerebration returned once the patient had begun to respond to command.

Ventilatory effects

The ventilatory effects of propofol were qualitatively the same as those seen with other i.v. agents (Gautier and Gaudy, 1978) and volatile agents such as halothane: a decrease in tidal volume, an increase in frequency, and a reduction in the inspiratory duty cycle ($T\text{I}:T^{tot}$ ratio). It is likely, therefore, that at least some of the changes are a consequence of the change in the state of the central nervous system between wakefulness and anaesthesia, rather than being a quantitative dose-related effect of a particular anaesthetic agent. These qualitative changes are not the same as those that occur during sleep (Stradling, Chadwick and Frew, 1985).

Some of the effects were more pronounced at the higher infusion rate of propofol, particularly the reduction in inspiratory duty cycle and ventilatory sensitivity to carbon dioxide, but the major change was between wakefulness and anaesthesia. Doubling the infusion rate did not double the effect. We do not know what it did to the concentrations of propofol reaching the brain.

One has to be careful when differentiating degrees of depression of the ventilatory response to carbon dioxide (Goodman and Black, 1985; Goodman and Curnow, 1985). Normally one compares the gradients of the responses rather than the intercepts on the $P\text{E}'_{CO_2}$ axis, because the intercepts are more sensitive to the technique of testing (Read and Leigh, 1967).

The slope of the ventilatory response to carbon dioxide is known to show considerable performance variability even in the same individual in the same state. Practical and ethical considerations limit the number of possible repetitions in each state in any one patient. The best one can achieve normally is to study a number of patients, each with one response in each state.

We had assumed from our previous work with conscious untrained subjects that the breath-by-breath scatter around the line of best fit of ventilation to $P\text{E}'_{CO_2}$, and the performance variability from one test to another, were both largely a result of being conscious. We were surprised to find that, in anaesthetized patients, there could still be a large scatter of breath-by-breath points around an individual response line, and that the occasional repetitions at the same state could produce quite different gradients. We are confident that these inconsistencies were not the result of technical errors such as leaks around the face mask. One can test easily for these by examining for a steady linear increase in carbon dioxide concentration on the paper trace. The other reason is that irregularities were not so much in the tidal volume as in the timing components of ventilation (Goodman and Black, 1987).

Carbon dioxide sensitivity varied widely between patients at both infusion rates, and overlapped the normal range of carbon dioxide sensitivity. There were presumably pharmacokinetic and pharmacodynamic differences between individuals and we do not know what contribution there may have been from the arousal caused by applying the face mask and possibly from the rebreathing itself. Intubation of the trachea is not the solution; during a previous study using Althesin (curtailed when the agent was withdrawn), an infusion that was sufficient to prevent movement to a surgical stimulus was not sufficient to prevent coughing during carbon dioxide rebreathing.

Even with the observed variability, and with the sample of only eight patients studied conscious and anaesthetized, carbon dioxide sensitivity was significantly less at the lower infusion rate than during consciousness; the gradient of the carbon dioxide response was depressed to 58 % of control, with 95 % confidence limits of ± 26 %. Doubling the infusion probably depresses the response by a further small amount, but we cannot put a confident figure on this, nor attach any statistical significance on the basis of our studies so far.

Assessments of $P\text{CO}_2$

It is easy to show, theoretically, that quite substantial decreases in carbon dioxide sensitivity are required before the carbon dioxide tension increases to clinically unacceptable values, and that halving the gradient of the carbon dioxide response, even with a 0.5-kPa increase in intercept, would result in a change of less than 1 kPa in arterial $P\text{CO}_2$. When tidal volumes were low, and in the absence of rebreathing, the $P\text{E}'_{CO_2}$ was probably an appreciable underestimate of the alveolar and arterial $P\text{CO}_2$. It is not surprising, therefore, that the measured reduction in carbon dioxide sensitivity could not be correlated with increases in $P\text{E}'_{CO_2}$.

Clinical conclusions

The ventilatory depression by propofol may be more pronounced than that of other agents used to the same end-point of anaesthesia. An induction dose of propofol is more depressant than an induction dose of thiopentone (Taylor et al., 1986). Halothane at 1 MAC depresses the ventilatory response to carbon dioxide to about 50 % of baseline. Originally described by Munson and colleagues (1966), this figure has been confirmed in later studies and equivalent depression occurs after a short infusion of thiopentone 3 mg kg^{-1} min^{-1} (Knill, Clement and Gelb, 1978). This is the same degree of depression that we found, but our results may not be directly comparable with those obtained with inhalation agents (Larson et al., 1969; Fourcade et al., 1971) as we cannot say that our infusion was a "1 MAC equivalent." Doubling the concentration of halothane to 2 MAC causes a further halving of the response to carbon dioxide: doubling the infusion rate of propofol did not do so.

The requirements of a clinical trial are strict—and sometimes unrealistically difficult. In clinical practice, we can choose whether or not to use premedication and adjuvant inhalation anaesthetic agents, and can adjust our induction and maintenance doses flexibly for the individual patient. The ventilatory depressant effects of propofol are undeniable, but are perfectly manageable in clinical practice and should not detract from the usefulness of this agent.

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INTER-RELATIONS OF THE VOLUME AND TIMING COMPONENTS OF VENTILATION DURING CARBON DIOXIDE REBREATHING IN AWAKE AND ANAESTHETIZED SUBJECTS

N. W. GOODMAN AND A. M. S. BLACK

SUMMARY

We studied the relations between the volume and timing components of ventilation during carbon dioxide rebreathing in conscious subjects and patients anaesthetized with propofol. In conscious responses, breath-by-breath minute ventilation ($\dot{V}_I$) generally correlated better with end-tidal carbon dioxide than did tidal volume (V_T), but V_T correlated better than $\dot{V}_I$ in the anaesthetized responses. The source of this difference was that, whereas V_T and the inspiratory period were both smaller and less variable when subjects were anaesthetized rather than conscious, the expiratory period was no less variable, and this disturbed the usual inverse relation between V_T and the duration of the ventilatory cycle. Anaesthesia stabilized the switch from inspiration to expiration, but not that from expiration to inspiration. In some patients, it produced a disturbance pronounced enough to suggest bimodality of the timing of expiration.

The volume and timing components of ventilation are usually measured as the tidal volume and the ventilatory rate, other ventilatory variables being derived from these. Ventilatory rate is estimated normally by counting over a number of breaths. The product of tidal volume and rate over a number of breaths is the ventilation over those breaths. The duration of the total respiratory cycle can be measured for a single breath; it is the reciprocal of the ventilatory rate for that single breath, the breath-by-breath frequency (f). The product of breath-by-breath f and breath-by-breath V_T is the breath-by-breath minute ventilation, $\dot{V}_I$. The total respiratory cycle (T^{tot}) is made up of the inspiratory period (T_I) and the expiratory period (T_E). The quotient V_T/T_I is the mean inspiratory flow rate (which will be termed IF and not $\dot{V}_I$ in this paper, to avoid confusion with $\dot{V}_I$).

Anaesthetists are used to considering some of these variables more or less formally when selecting an artificial ventilator, and adjusting it to control the ventilation of their patients. Respiratory physiologists use them formally and in more detail for describing spontaneous ventilation in conscious subjects and anaesthetized animals, but their application to spontaneously breathing anaesthetized patients has so far been relatively limited (Derenne et al., 1978; Gautier, 1980).

The breath-to-breath variability that occurs during spontaneous ventilation cannot occur during artificial ventilation because the variables are preset by the anaesthetist. This paper is concerned with the inter-relations of the *variabilities* of the volume and timing components of ventilation, comparing the patterns in conscious subjects and patients with the patterns in patients anaesthetized with propofol. The considerations arose from our study (Goodman, Carter and Black, 1987) of the effects of propofol on the conventional variables of ventilation: tidal volume, frequency, minute ventilation and the ventilatory response to carbon dioxide. It was prompted by the observation that, during carbon dioxide rebreathing under propofol anaesthesia, the response of breath-by-breath ventilation to the increasing carbon dioxide tension showed more scatter about its increasing trend than did the

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N. W. GOODMAN, M.A., D.PHIL., F.F.A.R.C.S.; A. M. S. BLACK, M.A., D.PHIL., F.F.A.R.C.S.; University Department of Anaesthesia, Southmead Hospital, Bristol BS10 5NB. Accepted for Publication: January 26, 1987.

response of tidal volume. We have made a preliminary report of our findings (Goodman and Black, 1986).

SUBJECTS, PATIENTS AND METHODS

Subjects and patients

Our results were from ventilatory responses to carbon dioxide obtained from 10 healthy awake volunteers and 12 patients anaesthetized with propofol. Eight of the volunteers were about to embark on a Himalayan expedition, and recording their ventilatory responses to carbon dioxide was part of an investigation of the causes of mountain sickness. The 12 patients (five male) were aged 22–64 yr and weighed 53–96 kg. All gave informed consent to the study, which was approved by the Hospital Ethics Committee. All were unpremedicated and had subarachnoid anaesthesia. General anaesthesia was maintained by an infusion of propofol alone while the subject breathed 100% oxygen via a face mask held carefully to avoid any leakage or entrainment (Goodman, Carter and Black, 1987). The ventilatory responses to carbon dioxide were tested at least once at one or both of two infusion rates of propofol: 100 or 200 $\mu g\ kg^{-1}\ min^{-1}$. Eight of the patients returned subsequently to have their responses tested when conscious.

Apparatus and data collection

The apparatus for the rebreathing manoeuvre (Read, 1967) was as described and used by Goodman, Carter and Black (1987). The principle is that a linearly increasing carbon dioxide stimulus is presented to the respiratory centres by having the subject rebreathe to and from a closed system while the response of ventilation is recorded. Although most of the data were obtained during ventilatory responses to an increasing carbon dioxide tension, non-stressed steady-state breathing was also recorded in a few patients. The same rebreathing apparatus was used, but it was primed with 100% oxygen and had a carbon dioxide absorber in the circuit to prevent the increase in carbon dioxide tension. The $F_{I_{O_2}}$ was greater than 60% for all of the recording periods.

Signals of end-tidal carbon dioxide tension ($P_{E'_{CO_2}}$) and tidal volume passed to a two-channel pen recorder (running paper speed 25 mm min^{-1}) and thence to an Apple IIe microcomputer for storage and analysis. Digital values for $P_{E'_{CO_2}}$, tidal volume (V_T), inspiratory time (T_I) and expiratory time (T_E) together with calibration values of P_{CO_2} and volume were stored on disc. The absolute limits of accuracy with our settings for the computer's analogue-to-digital convertor were 0.043% for carbon dioxide and 17 ml for volume. The program loop for collecting data ran at 30 Hz exactly, so timings were accurate to approximately 33 ms. Sighs and other very obviously abnormal breaths were deleted before analysis. We did not use a formal statistical test to reject these outliers, but did so from a visual inspection of the scatter plots. It was very unusual to have to reject more than two outliers from any particular response.

Statistical analysis

Regressions. The analysis was based on linear least squares regressions, the regression process being used in different ways for different purposes.

Regressions of $P_{E'_{CO_2}}$ on time could be done to check the linearity of the increase in carbon dioxide tension during the response. The response of ventilation to carbon dioxide was obtained by regressing breath-by-breath ventilation ($\dot{V}_I$) on $P_{E'_{CO_2}}$; the tidal volume response to carbon dioxide was obtained by regressing V_T on $P_{E'_{CO_2}}$. The response of ventilatory rate (f) to carbon dioxide was obtained by regressing f on $P_{E'_{CO_2}}$.

Regressions on elapsed time were performed for all the measured variables V_T, f, T_I, T_E, and the derived variables $\dot{V}_I$ and IF. The particular interest, for all the variables, was in their variability about any linear trend with time. We took the correlation coefficient (r) as the initial index of variability and investigated the variability further by examining the "time residuals".

Time residuals. The time residual of a variable for a particular breath is the difference between its measured value for that breath and the value indicated by the regression line of best fit to elapsed time. This is illustrated in figure 1 for V_T-time residuals and f-time residuals from a rebreathing manoeuvre in a conscious subject: the time residuals are the vertical lines joining the breath-by-breath data points to the line of best fit. The breath-by-breath time residuals were calculated for all the measured and derived variables except $\dot{V}_I$, and stored on computer disc.

The time residuals were used in three ways:
(i) Time sequence plots were examined visually for indications of major non-linearity during the response. Formal statistical tests were not applied (Draper and Smith, 1981).

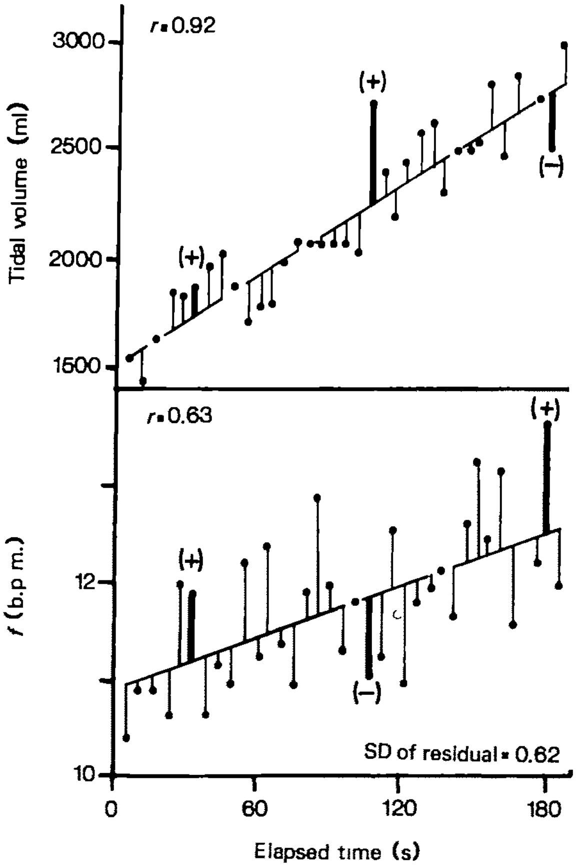

FIG. 1. Carbon dioxide rebreathing in a conscious subject: upper graph breath-by-breath tidal volume (*V*T) plotted against elapsed time; lower graph breath-by-breath ventilatory frequency (*f*) plotted against elapsed time. r = Correlation coefficient from least squares linear regression. The vertical lines joining the data points to the line of best fit are the "time residuals". In general, for each breath, larger-than-zero *V*T-time residuals (+) occur with smaller-than-zero *f*-time residuals (–) and *vice versa* (e.g. thick vertical lines at approximately 110 and 180 s), but this relation is not universal (e.g. thick lines at approximately 30 s.

(ii) The residual standard deviation (RSD), the square root of the averaged sum of squares of the residuals, was used as a measure of the overall variability of that ventilatory variable about its trend. If there is no trend, the RSD is the same as the standard deviation of the variable about its mean value.

(iii) The breath-by-breath residuals of one ventilatory variable about its trend were correlated with the breath-by-breath residuals for another to see how much of the about-trend variability of the first variable was related to that of the second. We were particularly interested in possible relationships between the about-trend variabilities of *V*T, *f*, *T*I and *T*E.

Other statistical procedures

The Fisher z-transformation was used to average correlation coefficients (*Documenta Geigy*, 1970). The Wilcoxon test for pair differences was used to compare groups of correlation coefficients for different ventilatory variables within the same responses, and to make within-patient comparisons in those eight patients from whom measurements were made in both the conscious and the anaesthetized states.

RESULTS

The first rebreathing manoeuvre from each conscious subject or patient was usually disturbed by unfamiliarity and other distractions of consciousness; it was used as practice, and the results were discarded. It was usually followed by two further responses which were technically satisfactory. All "anaesthetized" responses were analysed, provided that there were no obvious technical faults (Rebuck, 1976). In all we collected 19 satisfactory ventilatory responses to carbon dioxide from 10 volunteer subjects. Eight of the patients provided 13 responses when conscious and 15 while anaesthetized, and the remaining four patients were studied only when anaesthetized and provided eight responses. Thus there were 32

TABLE I. *Mean correlation coefficients (after z-transformation) of various variables, and their residuals against time, during carbon dioxide rebreathing awake and anaesthetized.* $\dot{V}_I$ = *breath-by-breath minute ventilation*; V_T = *tidal volume*; *IF* = *mean inspiratory flow*, f = *ventilatory frequency*, T_I = *inspiratory time*; T_E = *expiratory time. The correlation coefficients at levels of significance corresponding to 32 degrees of freedom are also shown*

	Awake	Anaesthesia
No. subjects	18	13
No. responses	32	23
Mean No. breaths	34.8	34.0
Correlation *v*. $P_{E'_{CO_2}}$		
$\dot{V}_I$	0.933	0.891
V_T	0.826	0.914
IF	0.940	0.919
*V*T-resid. *v*. *f*.-resid.	−0.526	−0.219
*V*T-resid.*v*. *T*I-resid.	0.601	0.411
*V*T-resid. *v*. *T*E-resid.	0.250	0.102
*T*I-resid. *v*. *T*E-resid.	0.196	0.025
r for $P < 0.05$	0.339	
$P < 0.01$	0.436	
$P < 0.001$	0.539	

"conscious" and 23 "anaesthetized" carbon dioxide responses (table I).

The numbers of breaths in each response ranged from 23 to 55, the mean and range being similar for conscious and anaesthetized responses. Most of the responses looked linear on superficial inspection.

Responses of ventilatory rate to carbon dioxide rebreathing

There was a significant positive correlation between frequency and $P\mathrm{E}'_{\mathrm{CO}_2}$ in 25 of the 32 awake responses, but in none of the anaesthetized responses. Even with a strong correlation, the actual increase in frequency was small.

Comparisons of variability around $\dot{V}\mathrm{I}$ and $V\mathrm{T}$ responses to carbon dioxide

In 26 of the 32 conscious responses, the ventilatory response to carbon dioxide ($\dot{V}\mathrm{I}$ *v.* $P\mathrm{E}'_{\mathrm{CO}_2}$) had a higher correlation coefficient than did the tidal volume response to carbon dioxide ($V\mathrm{T}$ *v.* $P\mathrm{E}'_{\mathrm{CO}_2}$). Correspondingly, the mean correlation coefficient (after *z*-transformation) for the $\dot{V}\mathrm{I}$ responses was 0.933 compared with 0.891 for the $V\mathrm{T}$ responses. Under anaesthesia, the opposite was true. In 20 of the 23 anaesthetized responses, the $V\mathrm{T}$ response showed a higher correlation coefficient than did the $\dot{V}\mathrm{I}$ response; the mean correlation coefficient of the $V\mathrm{T}$ responses was 0.914, compared with 0.826 for the $\dot{V}\mathrm{I}$ responses (table I).

These differences were tested formally for the eight patients who provided both conscious and anaesthetized responses. During consciousness the $\dot{V}\mathrm{I}$ responses adhered to the line of best fit significantly better than did the $V\mathrm{T}$ responses; and during anaesthesia they did so significantly less well ($P < 0.05$, Wilcoxon).

It is worth remarking that IF usually correlated with $P\mathrm{E}'_{\mathrm{CO}_2}$ at least as well as the better of $\dot{V}\mathrm{I}$ or $V\mathrm{T}$ — that is the correlation tended to be as good as that of $\dot{V}\mathrm{I}$ in the awake state, and as $V\mathrm{T}$ in the anaesthetized state.

Correlations between carbon dioxide and elapsed time

Regressions of $P\mathrm{E}'_{\mathrm{CO}_2}$ with time, when performed, showed correlation coefficients very close to unity unless there were technical problems such as leaks at the mouth. In valid responses, any deviations from the lines of best fit were mainly caused by errors in the $P\mathrm{E}'_{\mathrm{CO}_2}$ signal arising from the relatively limited precision of measurement, and from any difference between the recorded $P\mathrm{E}'_{\mathrm{CO}_2}$ and the actual central carbon dioxide stimulus to ventilation at that moment. We removed this variability by regressing the ventilatory variables on time rather than on $P\mathrm{E}'_{\mathrm{CO}_2}$; the fit of the trend with time was always better than the fit of the trend with $P\mathrm{E}'_{\mathrm{CO}_2}$. Consequently, when examining the variability of any time or volume component of ventilation about its trend, we always examined the variability about the trend with time: the time residuals.

TABLE II. *Significance of the correlation of the residuals of tidal volume* v. *time with the residuals of frequency* v. *time in rebreathing manoeuvres awake and anaesthetized*

Correlation	P	Awake	Anaesthesia
Negative	< 0.001	14	3
	< 0.01	9	6
	< 0.05	3	2
	ns	6	6
Positive	ns	0	3
	< 0.05	0	3
n		32	23

Correlations of $V\mathrm{T}$ *residuals with* f, $T\mathrm{I}$ *and* $T\mathrm{E}$ *residuals*

$V\mathrm{T}$ *and* f. There was a striking difference between conscious and anaesthetized responses (table II). Twenty-six of the 32 conscious responses showed significant ($P < 0.05$) negative correlations between the two sets of residuals. Significant negative correlations (< 0.05) were found in only 11 of the 23 anaesthetized responses. Correspondingly, the average correlation coefficient for the $V\mathrm{T}$ residuals against f residuals was -0.526 in the conscious responses and -0.219 in the anaesthetized responses (table I).

An inverse correlation between $V\mathrm{T}$ and f implies a direct correlation between $V\mathrm{T}$ and T^{tot}, and this was indeed the case.

$V\mathrm{T}$, $T\mathrm{I}$ *and* $T\mathrm{E}$. The major contribution to the direct $V\mathrm{T}$-to-T^{tot} relationship in both the awake and anaesthetized state was from that between $V\mathrm{T}$ residuals and $T\mathrm{I}$ residuals. This relationship was stronger in the conscious state; correlations significant at $P < 0.05$ were more frequent, and the averaged correlation coefficient was greater than while anaesthetized (table I). The correlations between $V\mathrm{T}$ and $T\mathrm{E}$ residuals were weaker and significant less frequently, especially under anaesthesia.

Overall there was no correlation between $T\mathrm{I}$

TABLE III. *Variability of four ventilatory variables during carbon dioxide rebreathing awake and anaesthetized. The values from responses for eight patients studied in both states are shown separately in the left-hand of the paired columns, and the right-hand of the paired columns includes those responses. RSD = residual standard deviation of the variable after correlation of that variable with time. Mean = average of the first five breaths recorded during the rebreathing manoeuvre. CV = Equivalent of coefficient of variation (RSD/mean × 100)*

	Awake		Anaesthesia	
	From eight patients also studied anaesthetized ($n = 13$)	All 32 responses	From eight patients also studied awake ($n = 15$)	All 23 responses
Frequency (b.p.m.)				
RSD	1.01	1.04	1.05	1.02
Mean	13.2	14.2	15.0	16.9
CV	7.5	7.2	6.9	6.3
Tidal volume (ml)				
RSD	107	135	42	38
Mean	1230	1250	630	600
CV	8.8	11.4	6.7	6.2
Inspiratory time (s)				
RSD	0.162	0.162	0.067	0.065
Mean	2.19	2.03	1.47	1.40
CV	7.1	8.0	4.5	4.6
Expiratory time (s)				
RSD	0.213	0.214	0.283	0.242
Mean	2.65	2.50	2.71	2.42
CV	9.3	9.0	10.7	9.7

residuals and T_E residuals, although correlation from eight conscious and two anaesthetized responses achieved significance. There was no association between those responses showing a significant correlation with those showing a relatively brisk response of ventilatory frequency during rebreathing.

The RSD of the ventilatory variables

The RSD is an index of the absolute variability about any trend during the response. It is useful to scale it somehow to the value of the variable itself. This we did crudely by relating it to the average value of the variable over the first five breaths of rebreathing, before it was too much affected by any trend. The quotient of the RSD and the mean value for each variable has some similarities to a coefficient of variation. It will be termed "CV", and is expressed as a percentage in table III.

Table III shows that the main differences between the state of consciousness and the state of anaesthesia with propofol are decreases in V_T and T_I, with an appreciable reduction in the variability of each about any trend they might show during a response. IF also decreases, as does its variability (not shown in table).

Time sequence plots

On visual inspection, the scatter of tidal volume and frequency residuals about their respective trends was usually symmetrical, with a range of variation that did not alter from the beginning to the end of the response. The exceptions were examined in detail, and gave us two types of information.

NL1: Non-linearity consistent with a tidal volume limitation. In one response from one conscious subject, the time sequence plot of V_T was obviously convex upwards, which was consistent with the tidal volume response to carbon dioxide being less steep at the end of the response. Ventilatory rate increased during the response, but there was no marked non-linearity. The correlation of $\dot{V}_I$ with $P_{E'CO_2}$ (or time) was stronger than the correlation of V_T with $P_{E'CO_2}$ (or time), and there was a weak but significant negative correlation between the V_T–time residuals and the f–time residuals.

A second-order polynominal regression gave a better fit between V_T and time, and the residuals from this regression gave a much stronger negative correlation between the V_T and the f residuals than there was for the residuals from the linear fit.

NL2: Cyclical non-linearity. The *V*T–time residuals and the *f*–time residuals from two of the anaesthetized responses seemed to cycle together around the zero line of their time sequence plots. Both of these responses gave *positive* correlations between the *V*T–time and *f*–time residuals, and one of these correlations was significant. Second- or third-order polynomial fits of both *V*T with time and *f* with time were marked improvements on the corresponding linear fits, and the positive correlation between the *V*T–time and *f*–time residuals was lost.

BM: Bimodality of ventilatory timing. One patient showed marked bimodality of ventilatory timing when anaesthetized, but not when conscious. All three of his anaesthetized responses gave plots of $\dot{V}$I against PE'$_{CO_2}$ that could not be fitted by a single straight line, although plots of *V*T against PE'$_{CO_2}$ could (fig. 2). On the paper recording of his ventilation during the operation, there seemed to be two populations of breaths: they had cycle lengths of either about 3.5 s or about 4.5 s. This bimodality was best seen in a plot of T^{tot} against elapsed time during a period of steady-state ventilation. In figure 3, T^{tot} is divided into *T*I and *T*E and shows that the bimodality of T^{tot} is caused apparently entirely by a bimodality in *T*E.

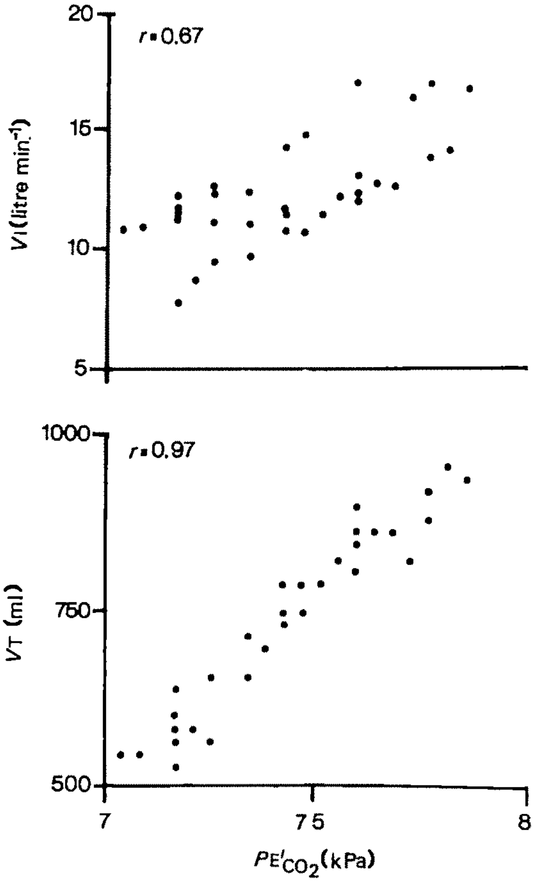

FIG. 2. Carbon dioxide rebreathing in an anaesthetized patient plotted in the upper graph as breath-by-breath minute ventilation against end-tidal carbon dioxide, and in the lower graph as tidal volume against end-tidal carbon dioxide. r = Correlation coefficient from least squares linear regression.

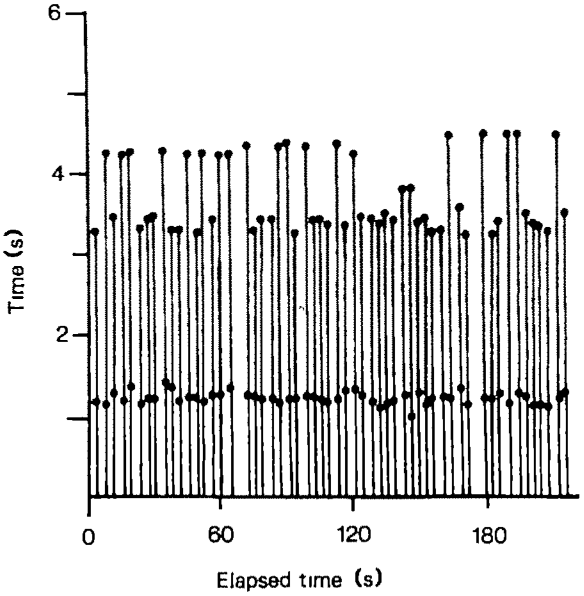

FIG. 3. Ventilatory cycle time during 3.5 min of steady-state ventilation in an anaesthetized patient. Each vertical line represents one breath and is divided to show inspiratory time (lower segment) and expiratory time (upper segment). The gaps at approximately 60 and 180 s are where single spurious breaths have been deleted.

There was a suggestion of bimodality in anaesthetized carbon dioxide responses from some of the other patients, but none was so obvious.

DISCUSSION

Ventilatory patterns during steady-state breathing

When ventilatory drive increases from one steady-state level to another, ventilation increases because of increases in both the average tidal volume and the average frequency. With carbon dioxide breathing, the *V*T effects predominate until *V*T approaches one-third to one-half of vital capacity (Hey et al., 1966; Clark and Von Euler, 1972; Gardner, 1977); after this point increases in

f make an increasing contribution. Increases in average V_T are brought about mainly by increases in average inspiratory flow over an unchanged or somewhat shortened average inspiratory time. Any increases in average f are brought about mainly by a reduction in average expiratory time (Kay, Strange Petersen and Vejby-Christensen, 1975; Newsom Davis and Stagg, 1975; Gardner, 1980). Thus if larger breaths are to be expired in a shorter time, the expirations are likely to need extra contributions from the expiratory muscles. These relationships *between the average values* of V_T and f in different steady-states must be distinguished from the relationships *between the variabilities about those average values* at any particular level of ventilatory drive.

When ventilatory drive is steady, mean inspiratory flow remains relatively steady from breath to breath (Priban, 1963; Newsom Davis and Stagg, 1975). Variations about the average T_I produce corresponding variations about the average V_T, as if the inspiratory phase is controlled in the mode of a constant flow generator with variable time cycling. (The reality is, of course, more complex: the inspiratory muscles generate a negative inspiratory pressure, and the inspiratory flow is not constant, but has a time profile determined by the resistance and compliance of the ventilatory system.) Longer than average inspirations result in larger than average breaths, and these in turn tend to be followed by longer than average expirations. (This implies that the expiration of the larger breaths is not assisted by any extra expiratory muscle force, and that the lung volume must return to FRC before the next inspiration can begin.) The net result of the variations in T_I and T_E is an inverse relationship between breath-by-breath variations in V_T and f, which acts as a simple "mechanical" within-breath self-regulating process tending to smooth out the breath-by-breath minute ventilation. This inverse relation between the variabilities of V_T and f is the converse of the relation between their average values at different, steady-state, levels of ventilatory drive.

During longer periods of undisturbed breathing, ventilation tends to oscillate around its mean steady-state level. There may be a number of superimposed oscillations with periods of a few minutes to an hour or so and, during such oscillations, V_T and f are as likely as not to be changing together. This probably reflects the operation of a number of between-breaths self-regulating processes as they "hunt" around a level of ventilatory drive appropriate to the level of metabolic activity. The underlying mechanism for this is more complex and involves central nervous processes which may be susceptible to change by anaesthesia.

Ventilatory patterns during steadily increasing drive

This study shows that many of the features of ventilatory pattern during different steady states of ventilatory drive apply also during the dynamic state when there is a constantly increasing ventilatory drive. When studying variability in the steady-state, one looks at the deviations of the ventilatory variables from their steady-state means. In this study, because the variables themselves were changing, we looked at the deviations from the trend, while the variable changed during a carbon dioxide rebreathing response. As with the discussion of ventilatory patterns in different steady states, one must distinguish between associations *between trends* and associations of *variability about trends*. For the rest of this discussion we shall be interested primarily in association between the about-trend variabilities.

For most responses a linear regression (Read, 1967) was perfectly adequate to establish the trend, that is the gradient of the line, and we used the correlation coefficient (r) as an index of variability about the trend, that is closeness of fit of a particular variable over the course of a response. Our use of correlation coefficients, rather than any other derived statistic, as our index of comparison of variability is valid, because comparisons were made within individual responses for the same breaths, and hence for identical numbers of degrees of freedom. It was coincidence that the mean number of breaths per response was similar for the conscious and anaesthetized responses, and this made some of the comparisons easier.

We observed that $\dot{V}_I$ followed its trend better than V_T during consciousness, but worse during anaesthesia. $\dot{V}_I$ and V_T are linked by a factor — f, the ventilatory frequency — so it is necessary to consider what relationship between them can be responsible for this observation. The first possibility to consider is that non-linearities of the $\dot{V}_I$ or V_T response to carbon dioxide may be responsible, and that the observation may be an artefact of applying linear regression analysis to non-linear processes. In a previous study (Goodman and Curnow, 1985), we applied polynomial regressions to ventilatory responses to carbon dioxide, and could thereby identify significant non-linearities when the original plots of $\dot{V}$I against PE$'_{CO_2}$ looked acceptably linear; however, the actual improvement in regression fit was usually marginal. In this study we applied polynomial fits only when our previous experience indicated that there was something to be gained from it.

If the ventilatory frequency is absolutely constant throughout a response, the $\dot{V}$I response is identical to the VT response, except that f acts as a universal scaling factor. The gradient of the $\dot{V}$I response is then the product of f and the gradient of the VT response. The correlation coefficients of the two responses must then be identical.

If VT and f both increase linearly during a response, then the scaling factor is also increasing, and the response of ventilation will then be non-linear. It will increase more steeply at the end of the response than at the beginning. For this reason, a linear fit to the $\dot{V}$I response might yield a poorer correlation coefficient than a linear fit to the VT response. However, even when a trend in f was seen, the actual change was small, and the resulting non-linearity was not very obvious; besides, increases in f *only* occurred in conscious patients, and in them $\dot{V}$I followed its trend *better* than VT — and did so irrespective of whether there had been a change in f.

In some circumstances, the increase in tidal volume might not be progressive throughout the carbon dioxide response, but might show a break point at some limit of tidal volume. The continuing increase in ventilatory drive might then be expressed as an increased f after the break point: the combination of the two non-linearities might then yield a linear ventilatory response to carbon dioxide and a better linear fit for breath-by-breath $\dot{V}$I than for breath-by-breath VT.

A marked effect of this sort was found in only one response, from a conscious patient (see Results, time sequence plots, NL1). When both $\dot{V}$I and VT were fitted by polynomial regressions, the fit to the breath-by-breath $\dot{V}$I was still better than the fit to VT, and the negative correlation between VT–time residuals and f–time residuals was stronger.

Thus non-linearities do not have a significant part to play in explaining our results.

Even if the ventilatory frequency does not increase, or decrease, consistently during a response, there will inevitably be breath-by-breath variation in f (and its reciprocal T^{tot}). If there were no relation at all between the variabilities about trend of VT and f, the general expectation would be that the about-trend variability of the product $\dot{V}$I of the variables VT and f should be *greater* than the variability of either VT or f. The situation seen in conscious patients is the opposite of this. It is the negative correlation between the about-trend variabilities of VT and f which offers the most likely explanation for this exception to the general expectation.

The simple mechanical within-breath self-regulating mechanism which holds ventilation to its mean value during the steady state also holds it to its trend during dynamic changes of ventilatory drive. It appears to be less effective during anaesthesia than during consciousness, and the reasons for this need some consideration.

There are three sources of about-trend variability of VT, TI, and TE. There is a contribution to real variability that is related to real variability in one or both of the others; there are contributions of real variability which are not related to real variability in the others; and there are contributions of variability which are related to errors of measurement. The size and significance of the correlation coefficients between the residuals of the different variables reflect the relative size of the first of these contributions.

During consciousness, the real about-trend variability of TI is appreciable. It makes an important contribution to the about-trend variability of VT when compared with the contributions of variability in mean inspiratory flow and the measurement errors in both VT and TI. Under anaesthesia, IF is less variable about its trend, TI is also less variable as well as being shorter; VT is less variable and smaller. The absolute measurement errors in VT and TI remain the same, so that they contribute relatively more to the total measured about-trend variabilities of VT and TI. Thus the VT-to-TI correlation is weaker under anaesthesia than during consciousness.

Similar considerations apply during the expiratory phase, but there is another important effect. During consciousness, the size of a particular breath tends to make some contribution to the duration of its expiration: lung volume takes longer than trend to return to FRC after tidal volumes that are bigger than trend, and the system seems to wait for the return to FRC before initiating the next inspiration. Thus the real, related variabilities of T_I, V_T and T_E make an appreciable contribution to their total measured variabilities. However, the effect does not appear to be as strong as during steady-state breathing and, under anaesthesia, it practically disappears.

This seems to be caused by the effect of propofol anaesthesia on the central clock-and-switch mechanisms which govern the changes between inspiration and expiration. The inspiratory phase is strikingly shortened. (It may be that the reduced variability can be explained by the absence of the distractions to which the conscious mind is susceptible.) However, the expiratory phase remains just as long and just as variable as during consciousness. Because of the shorter inspiration at reduced inspiratory flow, the tidal volume is smaller, and this tidal volume can always be expired in well under the time allowed by the timer for the expiratory phase. There tends to be a much more pronounced expiratory pause than during consciousness, and presumably the next inspiration is started by the central expiratory timer later than would be expected if it were simply a matter of having to wait for lung volume to return to FRC. In one clear case (see Results, time sequence plots, BM) the effect was more complex. Under propofol anaesthesia the expiratory clock changed abruptly and apparently randomly between one expiratory timing and another.

Limitations of method

During awake carbon dioxide responses, subjects and patients breathed through a mouthpiece; during anaesthetized responses patients breathed through a face mask. This may have altered the frequency and tidal volume of resting ventilation, but we do not think it influenced our analysis. Newsom Davis and Stagg (1975) used a face mask, and our analysis of the variabilities from stressed breathing are in agreement with theirs from the steady state. We do not know what contribution there may have been from the stimulus of holding a mask tightly to the face of our anaesthetized patients. We would have expected it to cause marked irregularities of both frequency and tidal volume, and perhaps marked non-linearities during rebreathing, but these were not seen.

Nor do we think that differences in the mean values of ventilatory variables between the awake and anaesthetized states were of much influence. The biggest differences were the larger tidal volumes when awake, and the smaller and slower increase in $P_{E'CO_2}$ during the anaesthetized responses. However, the differences in pattern were present also in those records of steady-state breathing that we looked at, not just during rebreathing.

On-line data collection and computer analysis are not necessary if all one wants to know is the ventilatory sensitivity to carbon dioxide, although it certainly eases the analysis, and the programs were written for this purpose. They are, however, the only feasible way of investigating breath-by-breath ventilatory patterns, but the questions raised in this study have stretched our present measuring capabilities and our programs to the limit of their useful accuracy (Newsom Davis and Stagg, 1975). For instance, the program measures time with a loop lasting 33 ms; this is accurate enough to calculate a simple ventilatory response, but we must expect a minimal error of about 1% in a T^{tot} of 3 s, 3% in a T_I of 1 s, and 30% or more in a T_I residual of 0.1 s or less.

We have been careful to avoid spurious correlations when dealing with derived variables. For instance, IF residuals showed significant negative correlations with T_I residuals in a number of responses. If this were real, it would suggest that there was a volume-limiting control — that is that faster breaths are also shorter, so that the final tidal volume is the same as with slower breaths because slower breaths are longer. The more likely explanation, however, is that the measurement errors in the T_I residuals have simply been regressed on their inverse, which is contained in the quotient V_T/T_I.

Such spurious correlations will not arise for measurements which are truly independent. The relatively limited resolving power of our present measuring capabilities leads us to expect that the estimates of significance which have emerged from our correlations are minimal estimates of the true strength of the relationships, and that when we pursue the investigation with improved equipment, more interesting relationships are likely to emerge. Because of the objectives and design of our algorithms for data collection, we were unable to study the inspiratory and expiratory flow profiles in detail. In particular, we could not measure accurately any inspiratory or expiratory pauses, although we were confident in our overall timings of inspiration and expiration.

Between-breaths self-regulating processes

We have concluded that the simple "mechanical" within-breaths self-regulating process which has been described for steady-state breathing operates also during the rebreathing manoeuvre although it is weakened during propofol anaesthesia by some interference with inspiratory and expiratory timing. There was no sign in conscious patients of any longer-term variation about the response trend. Perhaps when the ventilatory system is attempting to catch up with a progressively increasing drive, there is no opportunity for any "hunting" behaviour. The simultaneous variations of V_T and f about the response trend (Results, time sequence plots, NL2) may be an indication of such behaviour under anaesthesia, and two other anaesthetized responses from other patients were somewhat similar. However, these patients also gave other responses which did not show these features; they may simply have resulted from variations in arousal during relatively light anaesthesia.

Ventilatory responses to carbon dioxide by rebreathing do not last long enough to study the longer-term variations in the volume and timing components of ventilation, and they remain to be studied in steady-state breathing in anaesthetized man.

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CHANGES IN INTRAOCULAR PRESSURE ASSOCIATED WITH THE ADMINISTRATION OF PROPOFOL

B. VANACKER, D. DEKEGEL, J. DIONYS, R. GARCIA,
L. VAN EECKHOUTTE, G. DRALANTS AND J. VAN DE WALLE

SUMMARY

The effect of propofol on intraocular pressure (IOP) was measured in 25 patients presenting for elective non-ophthalmological surgery when propofol was used for the induction and maintenance of anaesthesia (together with 67% nitrous oxide in oxygen, and vecuronium). Normocapnia was maintained. After induction of anaesthesia, intraocular pressure was significantly lower than the baseline value; during maintenance IOP never exceeded the pre-induction value. There was a temporary decrease in arterial pressure after induction. In nine patients a cutaneous flush was observed and in seven patients there was discomfort on injection. Spontaneous movement in 20% and hiccup in 12% of the patients were observed at the time of tracheal intubation.

Propofol (2,6-diisopropylphenol) is formulated currently as an oil-in-water emulsion (Cummings et al., 1984). This investigation was undertaken to define the effects of propofol on intraocular pressure when given as a single bolus dose of 2 mg kg^{-1} i.v. to induce anaesthesia, and then subsequently as an infusion at a rate of 9 mg kg^{-1} h^{-1} to maintain anaesthesia.

PATIENTS AND METHODS

Twenty-five patients aged 20–60 yr were studied. All were graded as ASA I or II and were without known ophthalmic abnormalities. They presented for elective general or orthopaedic surgery during which intraocular pressure (IOP) was measured (in both eyes) with a Perkins applanation tonometer (Perkins, 1965). Each patient gave informed consent and the study was approved by the Hospital Ethical Committee.

Patients were premedicated with lorazepam 1 mg given by mouth 1 h before the induction of anaesthesia. In the anaesthetic room a 20-gauge cannula was placed in a vein on the dorsum of the hand or forearm. IOP was measured bilaterally on arrival in the operating room (T1); anaesthesia was induced with a bolus dose of 1% propofol 2 mg kg^{-1} i.v. injected over a mean time of 36.4 s (SEM ± 1.99). One minute later, vecuronium 0.1 mg kg^{-1} was administered and the lungs were inflated gently with an oxygen–nitrous oxide mixture ($F_{I_{O_2}}$ 0.33). Two minutes after the injection of the vecuronium, a continuous infusion of propofol 9 mg kg^{-1} h^{-1} was started using an Ivac 630 volumetric pump.

IOP was measured 1 min after induction (T2), 2 min after the injection of vecuronium (T3) and 2 min after the start of the continuous infusion of propofol (T4). After the larynx and the trachea were sprayed with 4% lignocaine, tracheal intubation was performed (between times T3 and T4). In order to maintain normal values of end-tidal carbon dioxide, ventilation was controlled with a Servo ventilator. Further measurements of IOP were made at 15 (T5) and 45 min (T6) after the start of anaesthesia. If the patient moved, the continuous infusion was supplemented by one or more bolus doses of propofol (up to 1 mg kg^{-1}). After the last IOP measurement (45 min) fentanyl 1–2 μg kg^{-1} was administered. Ten minutes before the end of surgery the infusion of propofol

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B. VANACKER, M.D., D. DEKEGEL, M.D., J. DIONYS, M.D., J. VAN DE WALLE, M.D., F.F.A.R.C.S. (Department of Anaesthesiology); R. GARCIA, M.D., L. VAN EECKHOUTTE, M.D., G. DRALANTS, M.D. (Eye Clinic); University Hospital St Pieter–St Raphaël, Brusselsestraat 69, B-3000 Leuven, Belgium.
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TABLE I. *Physical characteristics of the patients*

	Propofol
n	25
Sex ratio (M:F)	10:15
Age (yr) (mean ± SEM)	38.8 ± 2.4
Weight (kg) (mean ± SEM)	69.2 ± 2.0

was discontinued, and when the operation was finished, the nitrous oxide was discontinued and the patients allowed to breathe 100% oxygen.

Heart rate and arterial pressure were recorded at the time of IOP measurements and any side-effects occurring during the induction and maintenance of anaesthesia were noted. Statistical analyses were performed by Student's *t* test ($P < 0.05$).

RESULTS

Twenty-five patients (15 female) aged 20–60 yr and weighing 56–86 kg were studied (table I).

Figure 1 shows the changes in intraocular pressure at the different time points after induction, and during maintenance of anaesthesia, with propofol. One minute after the injection of propofol (T2), there was a significant decrease in IOP ($P < 0.001$) compared with the pre-induction value (T1). Administration of vecuronium resulted in a further decrease in IOP (T3). After intubation (T4) IOP increased, but the value remained less (statistically significant) than the pre-induction value. During maintenance (T5, T6), IOP was less than the baseline value, although the differences were not significant.

The administration of propofol 2 mg kg^{-1} was associated with significant decreases in arterial pressure (T2, T3). Tracheal intubation increased arterial pressure above the baseline value (T4) and also caused a significant increase in heart rate. Changes in arterial pressure and heart rate were minimal during the maintenance of anaesthesia with propofol (fig. 2).

Side-effects noted in the study are presented in table II. A cutaneous flush was observed in nine patients and seven patients experienced discomfort on injection. Spontaneous movement occurred in five patients and hiccup in three.

In all patients recovery after anaesthesia with propofol was rapid and smooth.

DISCUSSION

This study has demonstrated that propofol, in a dose of 2 mg kg^{-1}, produces a significant and

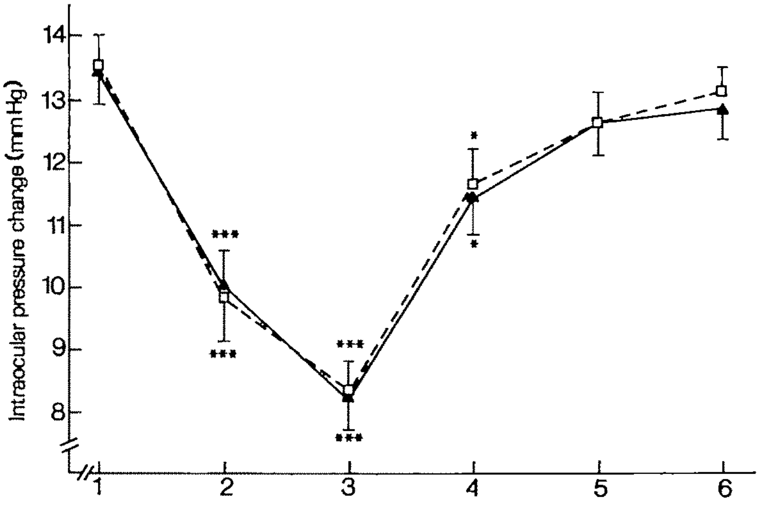

FIG. 1. Right (□) and left (▲) intraocular pressure changes (mean ± SEM) at different time points after administration of propofol: 1 = Pre-induction values; 2 = 1 min after induction with propofol 2 mg kg^{-1} (+bolus injection of vecuronium 0.1 mg kg^{-1}); 3 = 3 min after induction with propofol (+start of continuous infusion of propofol 9 mg kg^{-1} h^{-1}); 4 = 5 min after induction with propofol—intubation between 3 and 4; 5 = 15 min after start of anaesthesia; 6 = 45 min after start of anaesthesia *$P < 0.05$; ***$P < 0.001$.

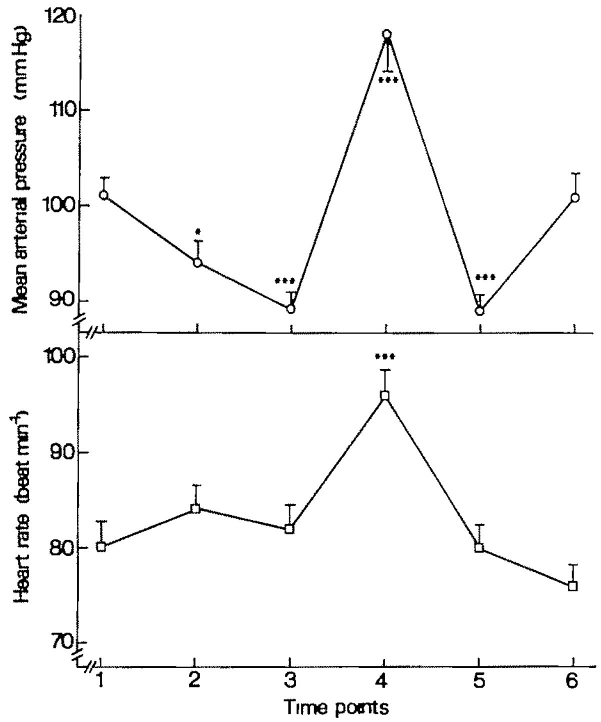

FIG. 2. Mean (± SEM) arterial pressure and heart rate changes at different times after administration of propofol · 1 = Pre-induction values; 2 = 1 min after induction with propofol 2 mg kg^{-1} (+bolus injection of vecuronium 0.1 mg kg^{-1}); 3 = 3 min after induction with propofol (+start of continuous infusion of propofol 9 mg kg^{-1} h^{-1}); 4 = 5 min after induction with propofol—intubation between 3 and 4; 5 = 15 min after start of anaesthesia; 6 = 45 min after start of anaesthesia. *$P < 0.05$; ***$P < 0.001$.

TABLE II. *Side effects*

	Propofol (n = 25)
Discomfort on injection	7
Cutaneous flush	9
Spontaneous movement	5
Hiccup	3

useful decrease in IOP. Other i.v. anaesthetic induction agents have been shown to cause decreases in IOP. Couch, Eltringham and Magauran (1979) observed a decrease in IOP after the induction of anaesthesia with thiopentone. The decrease in IOP was substantially the same as in our study. There was also a decrease in mean arterial pressure after the injection of thiopentone. From these results it cannot be clearly defined whether the observed decrease in IOP was attributable to the effects of propofol itself or was the result of the decrease in arterial pressure. In our study of patients younger than 60 yr, the injection of propofol was associated with significant decreases in arterial pressure, and this may have contributed to the reduction in IOP (Self and Ellis, 1977). When etomidate was used as an induction agent, a decrease in IOP was observed by Oji and Holdcroft (1979); however, they were not able to demonstrate a decrease in systemic arterial pressure.

In all these studies the applanation tonometric method was used (Perkins, 1965). This instrument was chosen because it uses the principle of applanation, which is more accurate than that of indentation tonometry with the Schiøtz tonometer (Kaufman, 1972). The end-point utilizes corneal patterns that must be properly centred to obtain an accurate reading. Applanation methods read directly the weight (in grams) needed to produce flattening of a given corneal area, and are directly convertible to mm Hg. The weight applied to the eye (0.5 g) is very small, and induces minimal increase in intraocular pressure. The result is not affected by the rigidity of the ocular coats (Schmidt, 1961).

In ophthalmic surgery, patients are ventilated electively; the administration of vecuronium immediately after the induction dose of propofol may contribute to the further decrease in IOP. These results confirm the study of Jantzen and co-workers (1986), but contrast with the increase in IOP recorded by Sia and Rashkovsk (1981) after injection of vecuronium. However, measurements were taken with a Schiøtz tonometer in that study. The use of suxamethonium should be avoided in intraocular surgery, as IOP increases for 10 min or more after injection of this depolarizing agent (Cook, 1981). Patients were normoventilated with a nitrous oxide–oxygen mixture, as measured by end-tidal carbon dioxide (Smitt, Aass and Elnemoto, 1981). Although the inhalation of nitrous oxide is not associated with any change in IOP (Holloway, 1980) the use of nitrous oxide should be avoided in patients in whom intravitreal injection of gas is planned (Wolf, Kapuano and Harding, 1983).

Following intubation there were increases in IOP in all the patients studied, but the values were still lower than the pre-induction control values. In our study a small dose of lorazepam was given as premedication, because large doses of benzodiazepines decrease IOP. Thus, the control value could be influenced if higher doses are used

(Al-Abrak, 1979). Better control of arterial pressure and heart rate at the time of tracheal intubation might have been obtained by the administration of fentanyl before the induction of anaesthesia. Low-dose fentanyl blunts the circulatory responses to tracheal intubation (Martin et al., 1982). During the continuous infusion of propofol, IOP did not exceed the control pre-induction values. Volatile anaesthetic agents were avoided in this study. Spontaneous movements and hiccup in lighter levels of anaesthesia might induce small increases in IOP in the patients (Greaves, 1958).

Induction of anaesthesia with propofol was associated with a significant and useful reduction in intraocular pressure. During i.v. anaesthesia with propofol, IOP did not exceed control values. In the context of this study propofol—when used to induce and maintain anaesthesia—appeared safe. However, it will be remembered that the patients studied did not have any ophthalmological pathology. Consequently, further studies may be indicated before these results can be extrapolated to such patients.

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EXTRADURAL BUPIVACAINE WITH SUFENTANIL FOR VAGINAL DELIVERY

A Double-Blind Trial

A. VAN STEENBERGE, H. C. DEBROUX AND H. NOORDUIN

SUMMARY

The combination of sufentanil with bupivacaine plus adrenaline given extradurally for pain relief during labour was studied in a double-blind trial. One hundred and twenty patients were randomly divided into three groups and received a 10-ml extradural injection of sufentanil 15 μg+bupivacaine 12.5 mg+adrenaline 12.5 μg, sufentanil 7.5 μg+bupivacaine 12.5 mg+adrenaline 12.5 μg, or bupivacaine 12.5 mg+adrenaline 12.5 μg (control group). A second injection, which was given upon request, was identical to the first. Subsequently, patients received a further 10 ml of bupivacaine+adrenaline, if required. The addition of sufentanil significantly decreased the latency, and increased the duration, of the analgesia. Moreover, the quality of analgesia was better and less bupivacaine was required, resulting in less motor blockade at delivery. There were no differences between the three groups in regard to Apgar scores. The only side effect of sufentanil was pruritis.

The usual concentration of bupivacaine given by the extradural route for relief of pain in labour is in the range 0.25–0.5%. However, 0.125% bupivacaine with adrenaline 1:800000 has been shown to produce satisfactory analgesia in most mothers throughout labour (Bleyaert et al., 1979) and has less effect on motor function.

Opioids injected to the extradural space act on specific receptors located in the substantia gelatinosa of the spinal cord and produce selective analgesia,—that is without affecting spinal nerve function (Camporesi and Redick, 1983; Justins et al., 1983; Cousins and Mather, 1984). While effective in many painful states, the use of extradural opioids alone in labour has been disappointing and it is necessary to use a dose comparable to that required for i.v. use; for example 100 μg of fentanyl. However, when combined with bupivacaine at the induction of extradural blockade, opioids produce better quality analgesia with a more rapid onset and a longer duration of action, when compared with the use of local anaesthetic alone (Justins et al., 1982; Van Steenberge, 1983; Youngstrom et al., 1984).

Data concerning postoperative analgesia have highlighted the advantages of sufentanil, a highly lipophilic agent (Donadoni et al., 1985). Compared with fentanyl, of which it is a derivative, its binding affinity to the opioid receptors of the mu type is greater and the normal i.v. dose for analgesia is 30 μg. When given by the extradural route, sufentanil produces analgesia (the quality of which is proportional to the dose) within 10 min, for a duration of about 6 h. Its main side-effect, which also is dose-dependent, in incidence and in duration, is sedation—which occurs at doses of 50 μg or greater.

The aim of this study was to evaluate, in a double-blind manner, whether the combined use of sufentanil 15 μg or 7.5 μg with 0.125% bupivacaine plus adrenaline by the extradural route:
(1) improved analgesia during labour and delivery;
(2) reduced the total dose of bupivacaine and the degree of motor blockade;
(3) had any unwanted effects on mother or baby.

PATIENTS AND METHODS

The design of the study was approved by the Hospital Ethics Committee. One hundred and twenty women who desired extradural analgesia

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A. VAN STEENBERGE, M.D.; H. C. DEBROUX, M.D.; H. NOORDUIN, Department of Anaesthesiology, Hospital St Anne, Place de la Vaillance 14a, Brussels, Belgium. Accepted for Publication: April 28, 1987

for delivery were randomly divided into three equal groups. An extradural catheter was inserted at either the L2–3 or L3–4 lumbar intervertebral space. They received an initial injection of 10 ml containing one of the following drug combinations:

group A: sufentanil 15 µg + bupivacaine 12.5 mg + adrenaline 12.5 µg;
group B: sufentanil 7.5 µg + bupivacaine 12.5 mg + adrenaline 12.5 µg;
group C: bupivacaine 12.5 mg + adrenaline 12.5 µg.

A second injection, which was given on the request for further analgesia, was identical to the first. Subsequently, but only if necessary, patients received a further 10 ml of bupivacaine 12.5 mg + adrenaline 12.5 µg. All the drugs were supplied in coded ampoules by Janssen Pharmaceuticals.

For the entire duration of labour, the parturient lay on her side, except during obstetric examination and extradural injection—which were performed in the supine position, with the uterus pushed manually to the left, or with the back slightly raised. If analgesia of the perineum was required an injection was made in the sitting position.

The times of injection and of the onset of analgesia were recorded. The patient's evaluation of the efficacy of the analgesia was assessed using the method of Bleyaert and colleagues (1979) which has a four-point scale of excellent, good, moderate and inefficient. At birth, motor block in the mother's abdominal muscles was assessed using a scale of total, marked, partial or no paralysis, according to the method of Van Zundert and colleagues (1984). The Apgar scores of the infants at 1 and 5 min were noted, as was the mode of delivery. The mothers were seen on the day after delivery for a general evaluation of the pain relief they had experienced which was graded as perfect, very good, good or insufficient, according to the stage of labour.

Because extradural analgesia makes the timing of the classical stages of labour difficult, we divided labour into a dilatation phase and an expulsion phase. The pain experienced during episiotomy was assessed in a similar manner.

All side effects were recorded and these included nausea, vomiting, pruritis, dizziness, headache and urinary retention.

Statistical analysis

Intergroup comparisons of continuous variables were made using Student's *t* test for independent samples: the Mann–Whitney test was used for scored variables, and the χ^2 test for nominal variables.

RESULTS

Of the 120 women taking part in the study, 13 were excluded for the following reasons: six underwent Caesarean section, the catheter was displaced in one, 1 coded ampoule was broken, three deliveries occurred soon after the first injection, and two inductions of labour were discontinued before labour was fully established.

The remaining 107 parturients formed three homogeneous groups of 37 (group A), 36 (group

TABLE I. *Patient data (mean ± SD). Significant differences from control*: *P < *0.05* (χ^2 *test*); †P < *0.05* (*Student's* t *test*)

	Group A Suf. 15 µg (*n* = 37)	Group B Suf. 7.5 µg (*n* = 36)	Group C Control (*n* = 34)
Age (yr)	27.0 ± 5.7	26.6 ± 4.7	28.3 ± 5.3
Weight (kg)			
Before pregnancy	60.5 ± 12.0	58.1 ± 8.4	58.2 ± 8.5
At term	73.9 ± 13.5	71.7 ± 11.1	69.9 ± 9.3
Duration of pregnancy (weeks)	39.2 ± 3.0	38.5 ± 6.6	39.4 ± 1.2
Primiparae	23*	21	13
Multiparae	14	15	21
Labour			
Spontaneous onset	12	15	14
Induced	25	21	20
Dilatation of cervix (cm)	3.3 ± 2.0	3.7 ± 3.3	2.9 ± 1.2
Contraction rate (min)	3.2 ± 1.6	2.8 ± 1.3*†	3.7 ± 1.9

TABLE II. *Results (mean ± SD).* *$P < 0.05$; ***$P < 0.001$

	Group A	Group B	Group C	Student *t* test	
	Suf. 15 µg	Suf. 7.5 µg	Control	A *v.* C	B *v.* C
Onset of analgesia first injection (min)	8.3±3.2	8.7±2.6	10.3±3.8	*	*
Duration of analgesia first injection (min)	129.8±59.6	131.4±44.9	85.8±35.6	***	***
Duration of labour first–last injection (min)	263±156	335±296	323±342	ns	ns
Bupivacaine requirement first–last injection ($mg\ h^{-1}$)	7.4±3.0	7.1±2.5	10.2±3.7	***	***

B) and 34 (group C) patients (table I). The only difference between the groups was in regard to parity: 23 and 21 of the women in groups A and B, respectively, were primiparae, against 13 in the control group.

The results concerning analgesia are given in tables II, III and IV. Sufentanil significantly reduced the onset time, although the difference was only about 2 min. However, the duration of analgesia produced by the first injection was 45 min longer (130 min) in the sufentanil groups compared with the control group (85 min). As a result the hourly dose of bupivacaine was smaller in the groups which received sufentanil. The statistical analysis of the quality of the analgesia showed significantly better results in the two groups which received sufentanil, on both the first and second injections.

General evaluation of the analgesia over the whole of labour is given in table V. Twenty-five of 36 women in group A, and 28 of 35 in group B, judged the analgesia to be "perfect" for the dilatation stage of labour against 18 of 34 in the control group.

TABLE III. *Quality of analgesia. Significant differences from control (Mann–Whitney* U *test):* *$P < 0.05$; **$P < 0.005$; ***$P < 0.001$

	Excellent	Good	Moderate	Insuf.
First injection				
Group A*** (suf. 15 µg)	33	3	—	1
Group B** (suf. 7.5 µg)	28	8	—	—
Group C (control)	17	10	6	1
Second injection				
Group A** (suf. 15 µg)	30	3	1	—
Group B* (suf. 7.5 µg)	29	5	—	2
Group C (control)	20	9	3	2

TABLE IV. *Delivery.* *$P < 0.05$ *compared with control (Student's* t *test)*

	Group A Suf. 15 µg	Group B Suf. 7.5 µg	Group C Control
Expulsion			
Spontaneous	22	24	21
Ventouse	15	12	13
Duration of expulsion (min) (mean ± SD)	11.9±7.1	11.7±8.0	10.4±8.6
Apgar score (mean ± SD)			
1 min	7.9±1.9**	8.1±2.1	8.8±1.3
5 min	9.5±0.8	9.8±0 7	9.6±0.7

TABLE V. *Global assessment of pain relief.* *$P < 0.05$ *compared with control (Mann–Whitney* U *test) Perfect = no pain at all; very good = short periods of pain, but still satisfied; good = longer periods of pain, but still satisfied; insufficient = not satisfied*

	Insuf	Good	Very good	Perfect
Dilatation				
Group A (suf. 15 μg)	—	2	9	25
Group B* (suf. 7.5 μg)	—	1	6	28
Group C (control)	1	2	13	18
Expulsion				
Group A (suf. 15 μg)	—	1	7	28
Group B (suf. 7.5 μg)	1	1	6	28
Group C (control)	—	3	8	23
Episiotomy				
Group A (suf. 15 μg)	3	—	4	25
Group B (suf. 7.5 μg)	2	1	2	28
Group C (control)	—	3	8	23

TABLE VI. *Motor blockade after delivery.* *$P < 0.05$ *compared with control (Mann–Whitney* U *test)*

	No.	Partial paresis	Marked paresis	Total paralysis of the legs
Group A* (suf. 15 mg)	22	13	1	0
Group B* (suf. 7.5 mg)	23	10	3	0
Group C (control)	12	16	6	0

For the expulsion stage the difference in evaluation was not significantly in favour of the groups that received sufentanil. The same results emerged in connection with episiotomy.

The use of sufentanil did not modify the duration of expulsion, nor the use of instrumental extraction (vacuum extractor only), the latter depending largely on the obstetrician's judgement. Apgar scores at 1 min were significantly lower in group A, but at 5 min they were equal in the three groups (table IV).

Motor blockade in the mother at delivery was significantly less marked in the two groups that received sufentanil (table VI), although no mother had total paralysis. Amongst the other unwanted effects, only pruritis could be attributed to sufentanil (table VII). It was not troublesome, remained mostly confined to the abdomen, and lasted 10–20 min. Sufentanil 15 μg had a higher incidence (43%) than 7.5 μg (22%). There was also an indication that dizziness was commoner with the higher dose.

TABLE VII. *Side-effects*

	Group A Suf. 15 μg	Group B Suf. 7.5 μg	Group C Control
Nausea	5	7	8
Vomiting	3	5	6
Pruritis	16	8	1
Dizziness	10	4	7
Headache	—	1	1
Urine retention	2	2	5

DISCUSSION

These results agree with those of previous studies in which bupivacaine and fentanyl were combined (Justins et al., 1982; Van Steenberge, 1983). Overall satisfaction was unquestionably superior, the onset of adequate analgesia was quicker, and the duration of the analgesia produced by the first injection was increased. Consequently, the hourly bupivacaine requirement was significantly reduced, and "top-up" injections were required less frequently (90–150 min compared with 45–90 min).

The less satisfactory results in the control group can be explained by the fact that, in most of the patients who rated analgesia as "good" rather than "excellent", a painful spot persisted on one side—presumably the result of a "missed segment". In addition, rapid dilatation and excessive contractions were not sufficiently relieved by a first injection of bupivacaine 12.5 mg and adrenaline.

The association of a small dose of sufentanil with a low dose of bupivacaine plus adrenaline, administered extradurally, offers a definite advantage in obstretric analgesia. It produces analgesia of long duration which rapidly attains excellence. This decreases the total dose of bupivacaine required, with a minimal degree of motor block at delivery and well maintained Apgar scores in the infant.

The unwanted effects of sufentanil are of no consequence and toxicity is negligible at the doses used. Thus the addition of an opioid allows relief of any residual pain resulting from an incomplete sensory block. While extradural opioid by itself is insufficient to relieve the pain of labour completely, it is quite effective in making up for any deficiency in the efficacy of the extradural blockade produced by local anaesthetics.

This additive effect of using two drugs, each with totally different sites and modes of action, has several potential clinical advantages. In particular, it will increase the effectiveness of the analgesia without increasing the risk of overdosage. In this way a low dose of each component of the mixture can be used.

While most centres in the United Kingdom use 0.25–0.5% bupivacaine for relief of pain in labour, we have for many years obtained reasonable results with 0.125%. This concentration rarely causes marked motor blockade and the risk of toxicity to either the mother or the baby is very low. However, the present study has shown that, in some mothers at least, the analgesia leaves something to be desired. By adding sufentanil the chance of failing to achieve good analgesia is greatly decreased. Our results would indicate that 7.5–15 μg of sufentanil per injection is quite sufficient in most patients; the normal i.v. analgesic dose is 30 μg.

The 40% prolongation of analgesia achieved in this study when sufentanil was added to bupivacaine has practical advantages because "top-up" injections are required less frequently and the dose of bupivacaine is reduced. This means that motor blockade is even less obvious than when 0.125% bupivacaine is used alone.

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INTRATHECAL SUFENTANIL AS A SUPPLEMENT TO SUBARACHNOID ANAESTHESIA WITH LIGNOCAINE

R. DONADONI, H. VERMEULEN, H. NOORDUIN AND G. ROLLY

SUMMARY

The combination of low-dose sufentanil with lignocaine for subarachnoid anaesthesia was studied in a double-blind comparative trial in 40 urological patients. Patients were allocated randomly to two groups and received 5% heavy lignocaine 1.5 ml together with either 1.5 ml of sufentanil 5 μg ml⁻¹, or physiological saline 1.5 ml. No statistically significant differences were observed between the two groups with respect to analgesia or anaesthesia. The only clear benefit of the addition of a low dose of sufentanil to lignocaine was the significantly longer period of postoperative analgesia. There was no significant difference in the number of patients requiring supplementary analgesics. Side-effects were similar in both groups.

Although subarachnoid anaesthesia is used frequently in association with urological surgery, it is not free from complications—such as severe cardiovascular depression (Greene, 1984). To avoid excessive sympathetic blockade and to retain, or even prolong, analgesia the usual dose of local anaesthetic may be reduced and the local anaesthetic itself replaced by an opioid (De Castro et al., 1980; Lecron, Toppet-Balatoni and Bogaerts, 1980; Cunningham, McKenna and Skene, 1983; Guerin et al., 1983). The aim of this study was to consider whether sufentanil, a more lipophilic and potent analgesic, and a better mu receptor ligand than fentanyl (Niemegeers et al., 1976; Leysen, Gommeren and Niemegeers, 1983), affected the degree of analgesia provided by the subarachnoid administration of lignocaine for urological procedures.

PATIENTS AND METHODS

Forty patients (ASA classes I, II and III) were included in the study, and were allocated randomly to two groups of 20 each. The design of the study was approved by the Ethics Committee of our institution, and every patient gave informed consent. All patients received diazepam 10 mg by mouth at 7.00 a.m. as premedication. Subarachnoid puncture was performed with the patient in the sitting position in the operating room after adequate preparation and once appropriate monitoring had been initiated. After a successful dural tap, 5% heavy lignocaine 1.5 ml together with 1.5 ml of a test solution was injected over 15–30 s and the patient placed supine immediately. The unmarked ampoules contained 2 ml of physiological saline or 2 ml of sufentanil 5 μg ml^{-1}.

The following variables were measured: arterial pressure, heart rate, ventilation rate, spread of anaesthesia to cold sensation (ether swab) and to pinprick before, and at 2, 5, 15, 30, 60, 90, 120, 180, 240 and 300 min after, the injection; spread of analgesia and anaesthesia only until full regression. The time interval to the first requirement for analgesia and the total amount of analgesia required following surgery were recorded also. The quality of anaesthesia was rated by the anaesthetist as excellent, good or inadequate.

The results were analysed by the Friedman two-way analysis of variance in each group and by Student's *t* test, the Mann–Whitney *U* test and the two-way analysis of variance for intergroup comparisons. A value of $P < 0.05$ was considered statistically significant.

R. DONADONI,* M.D.; H. VERMEULEN, M.D.; H. NOORDUIN; G. ROLLY, M.D.; Department of Anaesthesia, State University of Ghent, Belgium. Accepted for Publication: March 18, 1987.

*Address for correspondence: Department of Anaesthesia, Academic Hospital, De Pintelaan 185, B-9000 Ghent, Belgium.

TABLE I. *Patient data*

	Sufentanil ($n = 19$)	Placebo ($n = 19$)	Student t test
Sex (M/F)	17/2	18/1	
Age (yr)	67.8	63.7	ns
	(51–88)	(40–81)	
Weight (kg)	71.5	74.4	ns
	(47–94)	(61–101)	
Height (cm)	168.8	170.0	ns
	(150–185)	(160–183)	

TABLE II. *Type of operation*

	Sufentanil	Placebo
Trans urethral resection		
Bladder	5	7
Prostate	7	5
Cystoscopy + biopsy	4	2
Orchidectomy	2	1
Incision of bladder neck	—	2
Hydrocelectomy	—	2
Resection of epididimus cyst	1	0

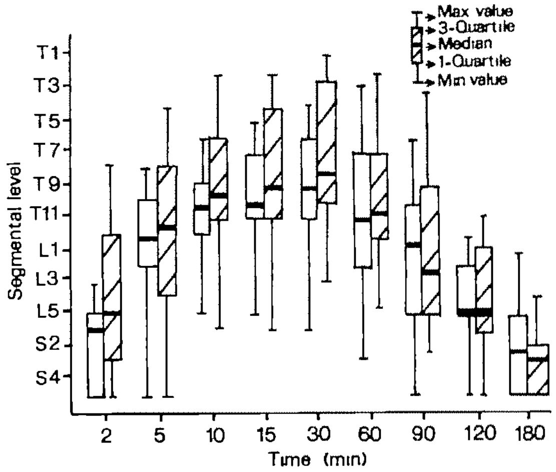

FIG. 1. Upper segmental level for anaesthesia to pinprick. (All figures: open columns = sufentanil; cross-hatched columns = placebo.)

RESULTS

The two groups were comparable with respect to age, weight and height (table I). The distribution of the different operations is shown in table II. In both groups one ampoule was accidently broken during opening, reducing both groups to 19 patients. The onset, progression and duration of analgesia and anaesthesia are shown in figures 1 and 2. In the sufentanil groups, analgesia was evident after 4.1 ± 3.8 (SD) min, reached its maximum spread at 30 min (median T8) and regressed in 3 h. Anaesthesia showed a similar pattern. In the placebo group, the onset of analgesia was noted after 2.3 ± 2.8 (SD) min, maximum spread was evident at 30 min and regression was complete after 3 h. The same results were observed for anaesthesia. In both groups, surgical anaesthesia for this type of operation lasted 60 min. No statistically significant differences were found between the two groups at any time for any of these variables.

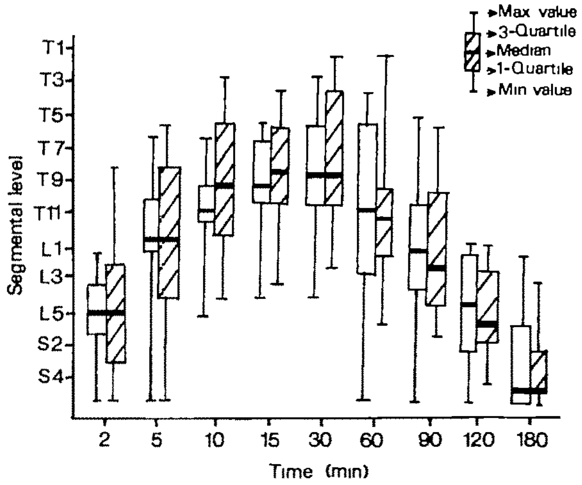

FIG. 2. Upper segmental level for anaesthesia to cold.

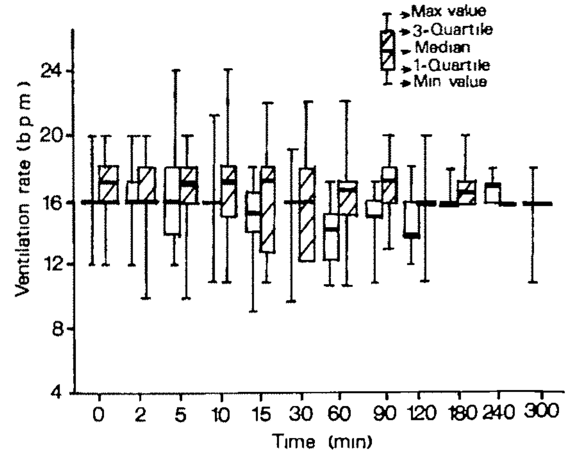

FIG. 3. Changes in rate of ventilation with time.

Systolic and diastolic arterial pressure (table III) decreased significantly ($P < 0.05$) in both groups during the development, and at the maximum spread, of the block. No significant differences were noted between the groups. Heart

TABLE III. *Cardiovascular data given as median values + first and third quartiles in parentheses. S = sufentanil* (n = *19*)*; P = placebo* (n = *19*). **P < 0.05 compared with time 0; †P < 0.05 between groups*

	Time (min)					
	0	2	5	10	15	30
Heart rate (beat min^{-1})						
S	82	79	75*	72*	67*	65*
	(75–85)	(75–90)	(62–80)	(65–80)	(65–75)	(60–74)
P	70†	70	70	70	66	67
	(60–80)	(62–80)	(60–75)	(60–75)	(60–70)	(60–72)
Systolic AP (mm Hg)						
S	132	135	130	117*	125*	117*
	(120–150)	(110–145)	(110–145)	(105–135)	(105–130)	(100–130)
P	127	130	120*	112	115*	117*
	(110–140)	(110–150)	(105–135)	(100–130)	(105–130)	(105–125)
Diastolic AP (mm Hg)						
S	80	80	80	75*	75*	75*
	(75–80)	(65–85)	(65–80)	(65–80)	(65–80)	(65–75)
P	80	82	72*	67*	70*	75
	(70–85)	(70–90)	(65–80)	(60–80)	(65–80)	(65–75)
	60	90	120	180	240	360
Heart rate (beat min^{-1})						
S	70*	77*	73*	73*	73*	75
	(63–75)	(60–85)	(60–85)	(62–80)	(60–80)	(65–80)
P	70	70	70	70	74	76
	(60–70)	(60–75)	(60–72)	(60–75)	(65–80)	(65–80)
Systolic AP (mm Hg)						
S	117*	120*	115*	125	120	136
	(110–130)	(110–135)	(110–135)	(115–140)	(110–140)	(110–150)
P	125	125	125	132	130	130
	(110–130)	(110–150)	(110–130)	(110–145)	(120–140)	(120–135)
Diastolic AP (mm Hg)						
S	75*	80	77	80	80	80
	(70–75)	(75–80)	(75–80)	(75–85)	(70–85)	(75–85)
P	80	80	80	85	85	82
	(70–80)	(75–90)	(70–90)	(75–90)	(80–90)	(75–85)

rate (table III) did not change in the placebo group, but decreased significantly ($P < 0.05$) in the sufentanil group. Ventilation rate (fig. 3) decreased significantly at 15, 60, 90 and 120 min in the sufentanil group, compared with the placebo group.

TABLE IV. *Side-effects*

	Sufentanil	Placebo
Itching	1	0
Headache	1	0
Sedation	3	4
Nausea	2	3
Vomiting	2	3
Bradycardia	6	7

Spinal blockade was inadequate in three patients in each group; it was excellent or good in all the others. Postoperative analgesia was requested by seven patients in the sufentanil group and by eight patients in the placebo group, but at different times: after 12.5 ± 7.0 (SD) h in the former and after 5.0 ± 2.4 (SD) h in the latter group ($P < 0.05$). The frequency of side-effects (table IV) was similar in both groups.

DISCUSSION

At the time of the study, no information was available about the optimal dose of sufentanil for intrathecal use. We arbitrarily chose 7.5 µg, based on the potency ratio between sufentanil and fentanyl (5–7:1), and previous experience with subarachnoid fentanyl in urology (Guerin et al., 1983).

No major difference between analgesia and anaesthesia was seen: the maximal spread, the quality of blockade and even the failure rate were identical in the two groups. These results suggest that anaesthesia was mostly, if not entirely, attributable to the action of the local anaesthetic. It is unlikely that the standard amount of lignocaine could be decreased as a result of the addition of sufentanil, as there was a 15% failure rate in both groups. This conclusion is at variance with the findings of Guerin and colleagues (1983) who, by adding fentanyl 50 µg, were able to decrease the amount of lignocaine to 25 mg. It is possible that the use of a more hypertonic solution, keeping the patient in the sitting position for at least 5 min after injection (not specified in the published study), or both, produced better blockade of the lower thoracic, and lumbar, segments. It is also possible that the dose of sufentanil used in our study was too low, given that the potency ratio of intrathecally administered opioids has been shown to be different from the normal i.v. ratio (Kitahata, Collins and Tatsumoto, 1984).

The mean thoracic level reached in our patients was as expected with the use of hyperbaric solution in patients placed in the supine position immediately after puncture (Wildsmith and Rocco, 1985). Rostral spread of analgesia in the sufentanil group was not seen, nor was this noticed after extradural administration in volunteers (Klepper, Sherril and Bromage, 1985). The cardiovascular responses were similar in the two groups. The significant difference in heart rate between the groups was merely the result of a higher preoperative rate in the sufentanil group. The similar incidence of episodes of bradycardia can be attributed to a local anaesthetic action on the sympathetic chain above the measured sensory level (Greene, 1984).

The initial decrease in the rate of ventilation was probably caused by a higher blood concentration of sufentanil after initial absorption into the blood stream, as has been shown after extradural administration (Camu et al., 1985). The later depression (from 60 min to 120 min) was possibly still attributable to a higher blood concentration as a consequence of a slower elimination process in the elderly. However, only one patient (and this patient only once) had a ventilation rate of less than 10 b.p.m. and, in the group as a whole, the effect on ventilation was minor. For this reason, and taking into account our previous experience after extradural sufentanil, it was decided not to perform blood-gas analysis.

The longer analgesic interval in the sufentanil group was the only clear benefit of this combination, but it was not supported by any significant reduction in the number of patients needing analgesic supplemention. After the first report (Donadoni et al., 1985) of the beneficial effect of extradural sufentanil in postoperative pain, others have confirmed this result. The pain-free period was of 4 h duration (Tan, White and Cohen, 1986; Van der Auwera, Verborgh and Camu, 1986) or even longer—6–9 h (Duckett et al., 1986; Naulty et al., 1986) with a low incidence of side effects, for doses from 30 to 100 µg. However, in all these studies sufentanil was given by extradural injection. No reports on intrathecal administration are available. Our results did not prove any beneficial effect of the subarachnoid administration of sufentanil in a dose of 7.5 µg during urological surgery. This dose is five to 10 times less than the dose given by the extradural route in the above mentioned reports. It is possible that the dose of sufentanil used was too small, and the ratio between extradural and spinal sufentanil is lower than 1:5 to 1:10, as is the case for morphine (Cousins and Mather, 1984).

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SIDE EFFECTS AND CHANGES IN PULMONARY FUNCTION AFTER FIXED DOSE PRECURARIZATION WITH ALCURONIUM, PANCURONIUM OR VECURONIUM

J. MOTSCH, W. FUCHS, P. HOCH, V. KAAS
AND K. HUTSCHENREUTER

SUMMARY

One hundred and sixty premedicated patients undergoing surgery were assessed for changes in pulmonary function and signs of partial neuromuscular blockade following precurarization with a fixed dose of alcuronium 2 mg, pancuronium 1 mg or vecuronium 1 mg, and the efficacy of the drugs in the prevention of suxamethonium-associated side effects was compared. In this respect, no differences were observed between the three drugs. Pretreatment with alcuronium and pancuronium was followed by small decreases in pulmonary function. Statistically significant changes were seen only when vecuronium 1 mg was used as the fixed-dose precurarization agent.

The administration of a small dose of non-depolarizing neuromuscular blocking agent before the injection of suxamethonium is used widely to prevent, or limit, the untoward side effects of suxamethonium. Variable success has been reported with this procedure in decreasing muscle fasciculations, postoperative muscle pain, and the frequency of cardiac arrhythmia (Jorgensen et al., 1980; Ferguson and Bevan, 1981; Ferres et al., 1983). However, precurarization itself is not free from unpleasant and serious reactions, and may result in changes in pulmonary function and neuromuscular transmission (Howardy-Hansen et al., 1980; Rao and Jacobs, 1980; Engbaek and Viby-Mogensen, 1984; Engbaek et al., 1985). Alcuronium has never been included in such studies and data with vecuronium have been published only for awake non-premedicated volunteers. In many hospitals "precurarization" implies the injection of a fixed dose of non-depolarizing blocking drug independent of the weight of the patient (Bennets and Khalil, 1981; Ferres et al., 1983; Engbaek and Viby-Mogensen, 1984).

The aim of this study was to compare the changes in pulmonary function caused by standard pretreatment doses of alcuronium 2 mg, pancuronium 1 mg and vecuronium 1 mg in premedicated patients immediately before surgery.

PATIENTS AND METHODS

One hundred and sixty patients (ASA grade I or II) undergoing elective surgery were studied. All were free from neuromuscular disease and had normal pulmonary function (Morris, Koski and Johnson, 1971). Written informed consent was obtained from each patient and the study was approved by the local Ethics Committee. The patients were randomly allocated to three groups (table I): 55 patients received a standard pretreatment dose of alcuronium 2 mg (group 1), 52 patients received pancuronium 1 mg (group 2), and 53 patients vecuronium 1 mg (group 3).

TABLE I. *Patient data (mean ± SD)*

	Alcuronium	Pancuronium	Vecuronium
n	55	52	53
Sex (M/F)	31/24	27/25	31/22
Age (yr)	36.5 ± 13.4	37.6 ± 12.3	33.9 ± 14.0
Weight (kg)	69.0 ± 11.1	68.8 ± 14.1	70.5 ± 10.9
Height (cm)	170.6 ± 7.9	170.5 ± 9.1	172.6 ± 8.6

JOHANN MOTSCH, DR. MED. UNIV.; WOLFGANG FUCHS, DR. MED.; PETER HOCH; VERONIQUE KAAS; KARL HUTSCHENREUTER, PROF. DR. MED., DR. MED. H.C.; Department of Anaesthesia, University of Saarland, D-6650 Homburg/Saar, F.R.G.
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TABLE II. *Frequency of suxamethonium-associated side effects after pretreatment with alcuronium 2 mg, pancuronium 1 mg or vecuronium 1 mg. Numbers in parentheses indicate well marked responses. No difference is statistically significant*

	Group 1 Alcuronium (n = 55)	Group 2 Pancuronium (n = 52)	Group 3 Vecuronium (n = 53)
Flush	13	14	13
Thorax	9 (1)	9 (2)	9 (2)
Abdomen	4 (0)	5 (1)	5 (1)
Shoulder	4 (0)	7 (1)	5 (0)
Fasciculations	39	44	37
Arms	10 (4)	18 (8)	11 (7)
Legs, feet	39 (6)	40 (13)	37 (10)
Thorax	3 (2)	6 (2)	2 (0)
Abdomen	1 (1)	3 (2)	2 (0)
Arrhythmia	8	13	13
Muscle pain	28	28	26
Neck	18 (2)	13 (0)	14 (1)
Back	15 (1)	19 (1)	19 (1)
Arms, shoulder	3 (0)	1 (0)	0 (0)
Thigh	1 (1)	3 (0)	3 (0)
Pharynx	0	2 (0)	0
Intercostal	4 (0)	3 (0)	4 (0)
Abdomen	4 (0)	3 (0)	2 (0)
Headache	5 (3)	6 (0)	4 (1)

Pulmonary function was determined using a digital spirometer with automated BTPS correction (Spirotron, Draeger AG (Knorpp, 1975)). The following indices were calculated from the flow–volume loops: peak expiratory flow (PEF), forced vital capacity (FVC), forced expiratory flow (FEF), forced expiratory volume at 0.5 s, 1 s, and 3 s, respectively ($FEV_{0.5}$, FEV_1, FEV_3).

The evening before the operation all patients were trained in the use of the spirometer and the resting values for the supine position were determined (measurement A). Thirty to 45 min after premedication with either droperidol–fentanyl and atropine, or pethidine and atropine, the patients were transferred to the anaesthetic induction room and placed in the supine position on an operating table. An i.v. infusion was started and the ECG continuously monitored. After registration of pulmonary function (measurement B) the pretreatment dose of neuromuscular blocking agent was injected. Two minutes later the patients were questioned about the following symptoms: heavy eyelids, blurring of vision, general discomfort, difficulty in speaking, breathing and swallowing. In addition, they were asked to lift the head and sustain this position for more than 10 s. Note was taken of any evidence of ptosis or signs of respiratory distress. Thereafter pulmonary function was measured again (measurement C). Anaesthesia was then induced with thiopentone 3–5 mg kg^{-1}, and after the administration of suxamethonium 1 mg kg^{-1} the trachea was intubated.

Evidence of side effects of suxamethonium was sought by at least three persons who scanned the whole patient for muscle fasciculations and the occurrence of a flush. Simultaneously, the ECG was carefully monitored for evidence of arrhythmia. The next day the patients were asked about muscle pain and headache, as well as about discomfort during the precurarization period.

Statistical analysis

The Wilcoxon rank-sum test for paired data, the Kruskal–Wallis test and the chi-square test were used in the form supplied by the *Statistical Package for Social Sciences* (Nie et al., 1975).

Significance was assigned at a level of 0.05.

RESULTS

The frequencies of suxamethonium associated side effects are listed in table II.

The appearance of a flush was restricted to small areas and was transient, persisting for more than 5 min in only 4% of patients. Changes in heart rate were also temporary and did not require any therapeutic measures. Frequent, but inde-

TABLE III. *Frequency of signs and symptoms of partial neuromuscular blockade occurring 2 min after fixed dose precurarization.* *P < 0.05 (*chi-square test*)

	Group I Alcuronium 2 mg (n = 55)	Group II Pancuronium 1 mg (n = 52)	Group III Vecuronium 1 mg (n = 53)
Signs			
Ptosis	38	44	49
Unable to open eyelids	10	10	24*
Difficulty in speaking	1	8*	11*
Difficulty in sustaining head lift	5	5	7
Unable to perform the pulmonary function test	1	2	0
Symptoms			
Heavy eyelids	40	50*	48*
Blurring of vision	14	15	19
Diplopia	17	21	22
Heavy tongue	4	4	9
Difficulty in swallowing	5	3	8
Difficulty in breathing	1	2	5
General discomfort	6	3	11

TABLE IV. *Changes in ventilatory function 2 min after standard pretreatment doses of alcuronium 2 mg, pancuronium 1 mg and vecuronium 1 mg.* *P < 0.05 (*Kruskal–Wallis test*)

	Group I Alcuronium 2 mg (n = 55)	Group II Pancuronium 1 mg (n = 52)	Group III Vecuronium 1 mg (n = 53)
PEF (litre s^{-1})	0.94±0.16	0.89±0.23	0.76±0.27*
FVC (litre)	0.96±0.08	0.91±0.14	0.81±0.18*
$FEV_{0.5}$ (litre)	0.94±0.17	0.93±0.28	0.79±0.34*
FEV_1 (litre)	0.95±0.09	0.91±0.16	0.81±0.21*
FEV_3 (litre)	1.00±0.09	0.91±0.13	0.82±0.17*
$FEF_{25-75\%}$ (litre s^{-1})	0.97±0.16	0.92±0.23	0.84±0.26*

pendent of the non-depolarizing drug in use, were fasciculations which occurred in more than 69% of patients. The frequency of marked fasciculation and muscle movement varied from 11% to 25%. There was no correlation between the localization of fasciculations and muscle pain. Muscle pain, in an extent to cause spontaneous complaint, was manifested mainly in the neck and the back. There were no statistically significant differences between alcuronium, pancuronium and vecuronium in their ability to prevent any of the side effects associated with suxamethonium. However, differences between the three non-depolarizing myoneural blocking agents did become obvious with respect to the frequency with which the side effects of precurarization itself were found (table III).

Significantly more patients in the pancuronium and vecuronium groups had difficulty in speaking, whereas the feelings of a heavy tongue and difficulty in swallowing were most pronounced in the vecuronium group. Difficulty in breathing was reported by one patient receiving alcuronium, by two patients receiving pancuronium, and by five patients receiving vecuronium, but only the three patients in the pancuronium and alcuronium groups were unable to perform the ventilatory function test after pretreatment. Premedication influenced only PEF. This change was evident in all groups, but was too small to achieve significance in the Kruskal–Wallis test.

There were statistically significant differences between the three neuromuscular blocking agents in their effects on ventilatory function (table IV).

Precurarization with alcuronium and pancuronium was followed by small decreases in PEF of 6% and 11%, respectively. The reductions in FVC amounted to 4% and 9%, those for FEV_1 to 5% and 9%, respectively. Significant changes

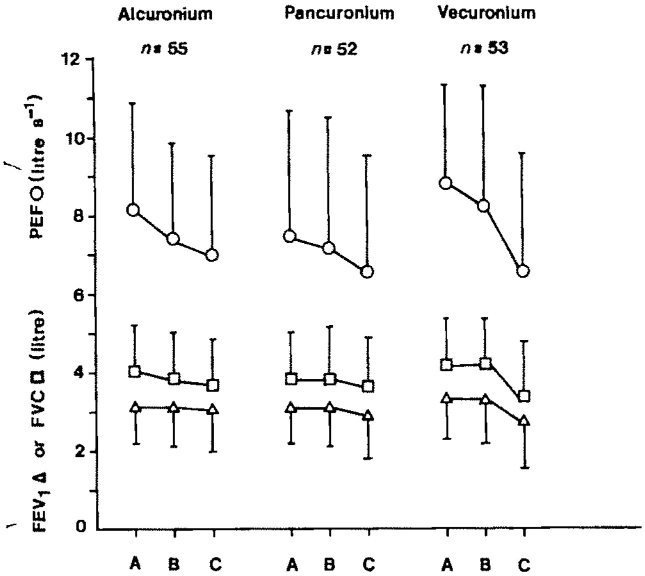

FIG. 1. Changes in ventilatory function (PEF, FVC, FEV_1), after premedication (measurement B) and 2 min after fixed-dose precurarization (measurement C) with alcuronium 2 mg, pancuronium 1 mg or vecuronium 1 mg. A statistically significant decrease was seen only with vecuronium 1 mg. Mean values ± SD. Measurement A = control values.

were seen only when vecuronium was used as the fixed dose precurarization agent. PEF was reduced by 24 %, FVC by 19 % and FEV_1 by 19 % (fig. 1).

DISCUSSION

Fixed dose precurarization with the three non-depolarizing neuromuscular blocking agents was successful in preventing severe suxamethonium-associated side effects, although a number of lesser manifestations still occurred. The pre-treatment itself, however, resulted in physical signs and symptoms of partial neuromuscular blockade, which produced a general feeling of discomfort in the patient and eventually impaired pulmonary function.

Of the ventilatory variables measured, PEF was reduced by 6 % with alcuronium, 11 % with pancuronium and 24 % with vecuronium. The reductions in FVC by alcuronium, pancuronium and vecuronium were 4 %, 9 % and 19 %, respectively, and those for FEV_1 were 5 %, 9 % and 19 %, respectively. Although the deterioration in ventilatory function was most obvious with vecuronium, two patients in the pancuronium group and one in the alcuronium group were unable to perform the pulmonary function tests at all following precurarization.

Premedication was included deliberately in the design of this study, in order to follow the usual local clinical routine, especially since most previous studies have been undertaken in healthy, unpremedicated volunteers. Howardy-Hansen and colleagues (1980) speculated that the frequency of general discomfort may be reduced by premedication. This view was supported by our findings, since the frequency of general discomfort was 6 %, which was in contrast to their report of general discomfort in 80 % of the patients receiving pancuronium 0.015 mg kg^{-1}, which is a dose similar to the standard dose, used in the present study, of 1 mg in a 70-kg person. The expectation put forward by Rao and Jacobs (1980), that ventilatory responses to precurarization may be aggravated by premedication, was not substantiated.

Pulmonary function was measured by us routinely 2 min after the injection of the non-depolarizing myoneural blocker. In view of the recent data by Agoston, Ket and Rashkovsky (1985), that the onset time of pancuronium and vecuronium is five times shorter than that of alcuronium (2 min *v.* 10 min), the time delay of 2 min as chosen by us may have been too short to permit the full development of partial curarization when alcuronium was used—although efficacy in preventing suxamethonium side effects was established.

Although there exists a tendency to rank the equivalent doses of the three drugs as 3 : 1 : 0.75 for alcuronium, pancuronium and vecuronium, pre-treatment doses of pancuronium 1 mg or alcuronium 2 mg, as used in the present study, are the most common clinical regimens (Ferres et al., 1983; Engbaek and Viby-Mogensen, 1984). Routine administration of a fixed dose of alcuronium 2 mg or pancuronium 1 mg seems to be a safe and clinically effective procedure. Vecuronium should be used in a dose of about 0.5–0.75 mg if preference is not for an exact dose per weight method and 0.01 mg kg^{-1} used. Nevertheless, patients should always be informed about possible side effects and, in view of the striking variation in individual sensitivity, it is important that the patient's reactions be carefully monitored and ventilatory support instituted immediately if needed.

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FLOW REQUIREMENTS AND REBREATHING DURING MECHANICALLY CONTROLLED VENTILATION IN A T-PIECE (MAPLESON E) SYSTEM

D. J. HATCH, A. P. YATES AND S. G. E. LINDAHL

SUMMARY

The influence of fresh gas flow (FGF) setting on rebreathing was investigated in 15 infants and children (weight 3.5–21.8 kg) during balanced anaesthesia with mechanically controlled ventilation using a T*-piece (Mapleson E) system and a Nuffield ventilator 200. Tidal volume (V_T), minute volume ($\dot{V}_E$), maximal inspired ($P_{I_{CO_2}}$) and end-tidal ($P_{E'_{CO_2}}$) carbon dioxide tensions and airway pressure were measured. $\dot{V}_E$, set to produce a $P_{E'_{CO_2}}$ of about 4.5 kPa and measured at a high FGF (minimal rebreathing), was unchanged throughout the study and the regression equation for V_E and weight was: V_E (ml min^{-1}) $= 146 \times \text{kg} + 482$, $r = 0.92$. Measurements were then repeated at FGF:V_E ratios reduced to 1.5 and 1.0. To achieve minimal rebreathing ($P_{I_{CO_2}}$ less than 0.5 kPa), FGF: $\dot{V}_E$ ratios greater than 1.8 (range 1.8–4.9) had to be used. At FGF: $\dot{V}_E$ ratios of 1.5, some alveolar rebreathing occurred, indicated by increased inspired ($P < 0.001$) and end-tidal ($P < 0.001$) carbon dioxide tensions. At FGF: V_E ratios equal to 1.0, alveolar rebreathing was more pronounced and hypercapnoea occurred with a $P_{E'_{CO_2}}$ (mean $\pm$ 1 SD) of 5.89 ± 0.53 kPa. At this FGF setting, change in I:E ratio from 1:2 to 1:1 did not influence the level of alveolar rebreathing. A minimal FGF (ml min^{-1}) setting of $1.5 \times V_E$ (that is, $1.5\ (146 \times \text{kg} + 482)$, approximated to the expression ($200 \times \text{kg} + 1000$) is recommended for controlled ventilation to avoid hypercapnoea when using the* T*-piece system in children weighing less than 20 kg.*

The fraction of fresh gas flow useful for gas exchange during mechanically controlled ventilation in partial rebreathing systems is equal to alveolar ventilation (Conway, 1976). This is, however, difficult to estimate in clinical practice. Non-alveolar rebreathing affects only deadspace and is not likely to affect end-tidal or arterial carbon dioxide tensions. If, on the other hand, alveolar rebreathing occurs, the end-tidal carbon dioxide tension increases.

During mechanically controlled ventilation in T-piece systems the fraction of fresh gas flow that participates in gas exchange varies with minute ventilation ($\dot{V}_E$) and with fresh gas flow (FGF) (Nightingale, Richards and Glass, 1965; Conway, 1976; Rose and Froese, 1979). Froese and Rose (1982) made recommendations for FGF and $\dot{V}_E$ designed to produce predictable arterial carbon dioxide tensions in children weighing between 10 and 30 kg.

In order to evaluate the degree of alveolar rebreathing at different FGF in infants and young children ventilated in a partial rebreathing system, and to test the recommendations made by Froese and Rose (1982), inspired and end-tidal carbon dioxide tensions were measured at different fresh gas flow settings and at various inspiratory:expiratory (I:E) ratios. Minute ventilation and ventilatory rate were kept constant throughout the study.

PATIENTS AND METHODS

Fifteen children weighing between 3.5 and 21.8 kg underwent a variety of surgical procedures.

David J. Hatch, M.B., B.S., F.F.A.R.C.S.; Alan P. Yates,* M.B., B.S., F.F.A.R.C.S.; Sten G. E. Lindahl,† M.D., Ph.D.; Department of Anaesthesia, The Hospital for Sick Children, Great Ormond Street, London WC 1N 3JH.

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Present addresses:

*Department of Anaesthesia, University College Hospital, Gower Street, London WC1E 6AU.

†Department of Anesthesiology, Mayo Clinic, Rochester, MN 55905, U.S.A.

Infants weighing less than 10 kg were premedicated with atropine 0.1–0.2 mg i.m. 30–60 min before the induction of anaesthesia. Those with body weights between 10 and 15 kg received pethidine compound 0.07 ml kg^{-1} i.m. (1 ml contains: pethidine 25 mg, promethazine 6.25 mg and chlorpromazine 6.25 mg), 60–90 min before arrival in the anaesthetic room. For children weighing more than 15 kg, papaveretum 0.4 mg kg^{-1} and hyoscine 0.008 mg kg^{-1} were given i.m. 60–90 min before induction. Anaesthesia was induced with oxygen in cyclopropane ($F\mathrm{I}_{\mathrm{O_2}}$ 0.5) and maintained with oxygen–nitrous oxide ($F\mathrm{I}_{\mathrm{O_2}}$ 0.5) with halothane or fentanyl, or both. Intubation of the trachea was facilitated with suxamethonium. Tubocurarine was used to ensure neuromuscular blockade during surgery. Further patient data are given in table I. The study was approved by the Hospital Ethical Committee.

The measuring apparatus was placed in the deadspace of the breathing system. Tidal volume ($V\mathrm{T}$) was measured by integration of the flow signal from a heated pneumotachograph (Fleisch No. 0) and a differential pressure transducer (Validyne MP 45-1-36, range ± 2 cm H_2O). Minute ventilation ($V\mathrm{E}$) was calculated from $V\mathrm{T}$ and the ventilatory frequency. Maximal inspired carbon dioxide tension (that is, the highest carbon dioxide tension that could be measured during inspiration ($P\mathrm{I}_{\mathrm{CO_2}}$)) and end-tidal carbon dioxide tension ($P\mathrm{E}'_{\mathrm{CO_2}}$), were measured by an in-line capnometer (Hewlett–Packard 14360A). Airway pressures were measured at the tracheal tube connection with a Druck pressure transducer (PDCR-75). Flow, volume, pressure and carbon dioxide signals were recorded on an ink-jet recorder (Siemens Elema, EM81). Flow and volume were calibrated by an accurate pump at 50 ml s^{-1} and at 30 ml, respectively, and the capnometer was calibrated using a known carbon dioxide tension. Because of interference with the infra-red spectrum by nitrous oxide and oxygen, the carbon dioxide signal was automatically corrected by the capnometer. The deadspace of the system was 8 ml measured by water displacement, which is similar to a T-piece system with an ordinary catheter mount, and the resistance was 1.4 kPa $litre^{-1}$ s^{-1} at a flow rate of 12 litre min^{-1}. ECG was monitored routinely on an oscilloscope, and arterial pressure was measured by an oscillometric technique (Dinamap, Applied Medical Research, Tampa, Florida, U.S.A.).

Procedure

The lungs of all children were mechanically ventilated with a Nuffield 200 ventilator fitted with the Newton paediatric valve (Newton, Hillman and Varley, 1981). $\dot{V}\mathrm{E}$, $V\mathrm{T}$, maximal inspired ($P\mathrm{I}_{\mathrm{CO_2}}$) and end-tidal ($P\mathrm{E}'_{\mathrm{CO_2}}$) carbon dioxide tensions and airway pressures were measured at different FGF and ventilator settings. Inspired oxygen and inspired as well as expired halothane concentrations were measured intermittently (Servo Multigas Analyser, Siemens Elema, Stockholm, Sweden). The Nuffield 200 ventilator was attached to the expiratory limb (length 1.1 m,

TABLE I. *Patient data*

Patient No.	Age (yr/month/day)	Body weight (kg)	Diagnosis	Operation
1	3/0/23	12.5	Renal pelvic obstruction	Pyeloplasty
2	4/6/6	15.5	Congenital deformity of hand	Correction
3	6/11/30	21.8	Syndactyly left hand	Correction
4	2/4/2	12.2	Bilateral undescended testicles	Orchidopexy
5	0/2/0	3.7	Hydronephrosis	Nephrectomy
6	3/7/24	15.6	Leukaemia	Bone marrow aspiration. Lumbar puncture. Insertion of Hickman's catheter
7	0/1/28	5.0	Hydronephrosis	Nephrectomy
8	2/11/24	12.2	Congenital dislocation of hip	Femoral osteotomy
9	0/3/0	6.2	Hydrocephalus	Ventriculo–peritoneal shunt
10	0/3/20	5.5	Achalasia	Fundoplication
11	5/2/14	16.3	Squint	Correction
12	0/3/29	3.5	Congenital cataract	Intraocular lens aspiration
13	1/1/23	9.5	Cleft palate	Repair
14	1/2/25	9.5	Urethral valves	Nephrectomy
15	1/0/13	8.7	Syndactyly right hand	Correction

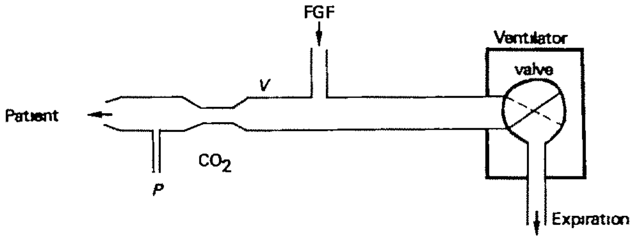

FIG. 1. Schematic presentation of the system and equipment used. P = position for measurements of airway pressure; CO_2 = in-line carbon dioxide meter and $\dot V$ the heated pneumotachograph. FGF = fresh gas flow.

width 2.2 cm) of a conventional T-piece system (Mapleson E system) (fig. 1). Ventilation volumes were initially set to give an end-tidal carbon dioxide tension of 4.5 kPa. The tidal volumes required to achieve this level of ventilation were measured and then kept unchanged throughout the study by adjusting the flow rate of the ventilator. The ventilatory frequency was 20 cycles per minute at all settings.

The first measurements were made at a fresh gas flow set high enough to minimize rebreathing; that is, to avoid significant alveolar rebreathing by keeping $P_{I_{CO_2}}$ less than 0.5 kPa, at an I:E ratio of 1:2. After the initial measurements FGF was reduced to 1.5 times $\dot V_E$ and measurements were repeated. Measurements were again repeated at an FGF setting equal to $\dot V_E$ still with an I:E ratio of 1:2. In 11 patients there was time for another set of measurements; in these, the I:E ratio was changed from 1:2 to 1:1 at the FGF:$\dot V_E$ ratio of 1.

No measurement was made until at least 30 min had elapsed since induction of anaesthesia and the ventilator setting had been unchanged for at least 20 min. Twenty minutes were allowed for equilibration between different settings before new measurements were made.

Statistics

Mean values and standard deviation (SD) were calculated. Results were evaluated with paired t test and probability values less than 0.05 were considered to indicate statistical significance.

RESULTS

During the different measurements mean arterial pressures and heart rates were similar (table II).

TABLE II. *Mean values (±SEM) of mean arterial pressure (MAP) and heart rate at a high gas flow (range 1.8–4.9 times $\dot V_E$ with a mean value of 3 × $\dot V_E$), at 1.5 × $\dot V_E$ at 1.0 × $\dot V_E$ with an I:E ratio of 1:2 as well as at 1.0 × $\dot V_E$ (n = 11) at an I:E ratio of 1:1 (1.0 $\dot V_E$, 1:1)*

	3 × $\dot V_E$	1.5 × $\dot V_E$	1.0 × $\dot V_E$	1.0 × $\dot V_E$, 1:1
MAP (mm Hg)	76±11	77±11	78±13	74±11
Heart rate (beat min^{-1})	130±32	134±34	138±30	136±37

TABLE III. *Mean values (±1 SD) of peak airway pressure (P_{aw}), highest inspired carbon dioxide tension ($P_{I_{CO_2}}$) and end-tidal carbon dioxide tension ($P_{E'_{CO_2}}$) at a high fresh gas flow (range 1.8–4.9 times $\dot V_E$ with a mean value of 3 × $\dot V_E$), at 1.5 × $\dot V_E$, at 1.0 × $\dot V_E$ with an I:E ratio of 1:2 (n = 15) as well as at 1 0 × $\dot V_E$ (n = 11) at an I:E ratio of 1:1. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ for differences between different settings of fresh gas flow and I:E ratio*

	3 × $\dot V_E$	1.5 × $\dot V_E$	1.0 × $\dot V_E$	1.0 × $\dot V_E$, 1:1
P_{aw} (mm Hg)	1.82±0.27*	1.75±0.29	1.73±0.30 (n = 15) 1.69±0.29 (n = 11)**	1.55±0.28 (n = 11)
$P_{E'_{CO_2}}$ (kPa)	4.49±0.24***	5.12±0.39***	5.89±0.53 (n = 15) 5.98±0.52 (n = 11)	6.15±0.65 (n = 11)
$P_{I_{CO_2}}$ (kPa)	0.31±0.14***	1.41±0.41***	2.54±0.49 (n = 15) 2.60±0.52 (n = 11)	2.71±0.64 (n = 11)

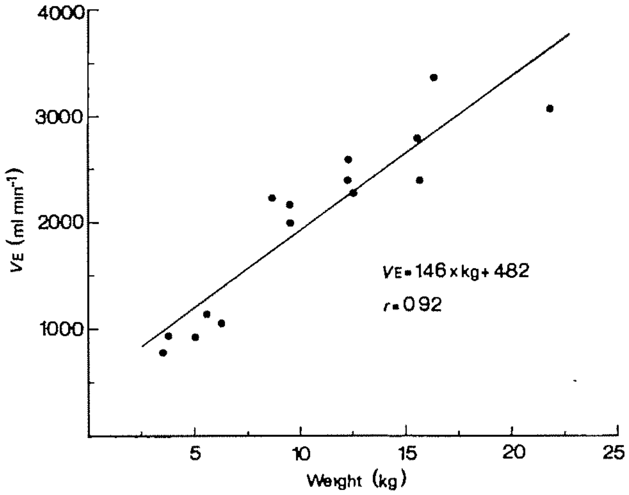

FIG. 2. Relationship between minute ventilation ($\dot{V}$E) and weight (kg) in the 15 children resulting in a $P\text{E}'_{CO_2}$ of about 4.5 kPa with negligible rebreathing. Regression equation and coefficient of correlation are given.

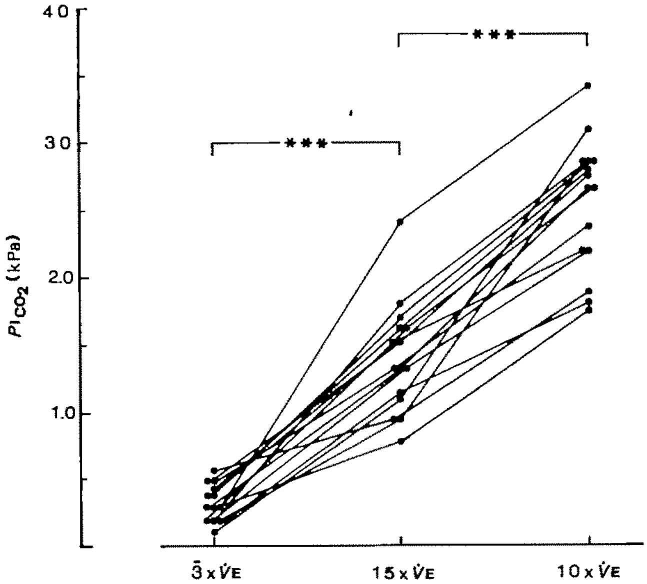

FIG. 3. Maximal inspired carbon dioxide tension ($P\text{I}_{CO_2}$) in each child at high fresh gas flow settings (3 × $\dot{V}$E) and at fresh gas flow settings of 1.5 and 1.0 times $\dot{V}$E. ***$P < 0.001$ for the differences indicated.

The peak airway pressure (P_{aw}) required to produce an end-tidal carbon dioxide tension of about 4.5 kPa (mean value ± 1 SD: 4.5 ± 0.2 kPa), during high FGF was 1.82 ± 0.27 kPa (mean ± 1 SD). At an FGF of 1.5 times minute ventilation, P_{aw} decreased to 1.75 ± 0.29 kPa ($P < 0.05$), although tidal volumes and ventilatory rates were unchanged (table III). There were, however, no changes in P_{aw} when the FGF was decreased from 1.5 to 1.0 times $\dot{V}$E (table III). In the 11 children who were also studied at an I:E ratio of 1:1, P_{aw} decreased from 1.69 ± 0.29 kPa at an I:E ratio of 1:2 to 1.55 ± 0.28 kPa ($P < 0.01$) at 1:1; tidal volumes and ventilatory rates were unchanged.

The relationship between $\dot{V}$E and weight during the study was described by the regression

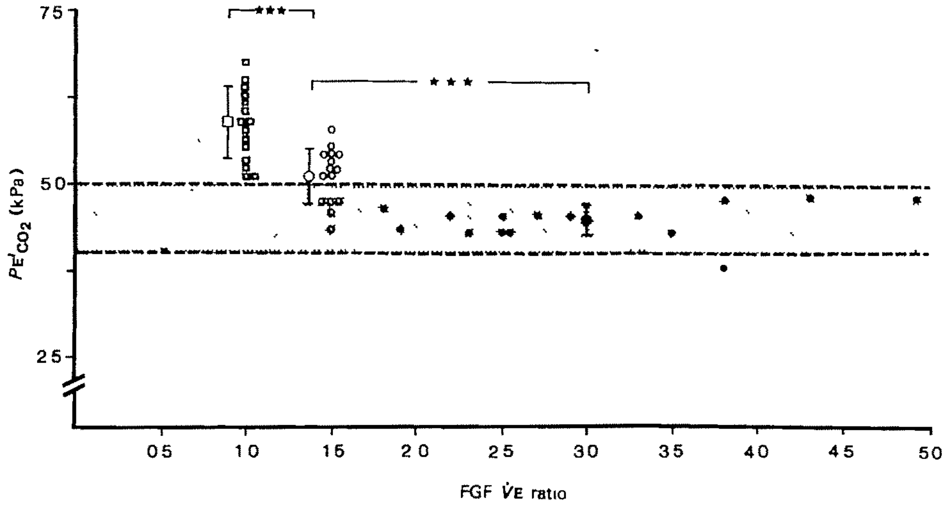

FIG. 4. End-tidal carbon dioxide tensions ($P\text{E}'_{CO_2}$) at different FGF : $\dot{V}$E settings. Filled circles represent data from high fresh gas flow settings with minimal rebreathing, open circles show $P\text{E}'_{CO_2}$ values at 1.5 × FGF : $\dot{V}$E and open squares at 1.0 FGF : $\dot{V}$E. Large filled and open circles and squares indicate mean values (±1 SD). Shaded area shows a $P\text{E}'_{CO_2}$ range between 4.0 and 5.0 kPa. ***$P < 0.001$ for the differences indicated.

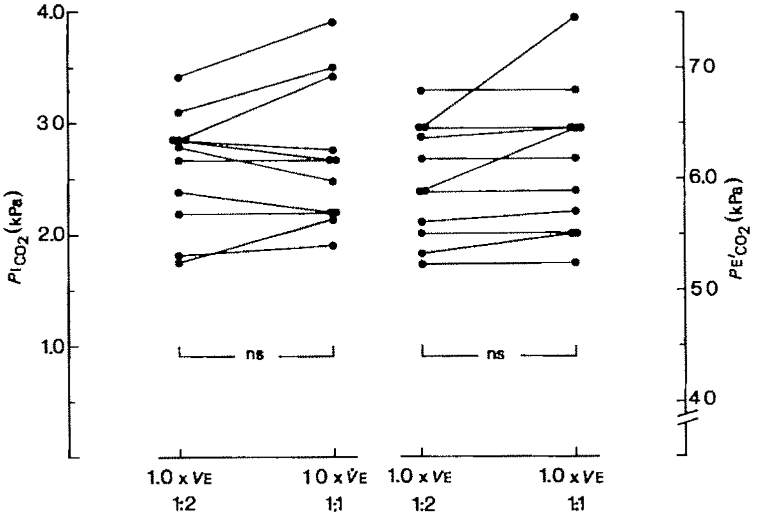

FIG. 5. Maximal inspired ($P\text{I}_{CO_2}$) and end-tidal ($P\text{E}'_{CO_2}$) carbon dioxide tensions in each individual at a fresh gas flow setting of 1.0 × $\dot{V}$E with an I:E ratio of 1 : 2 and 1 : 1. There were no statistically significant differences.

equation: $\dot{V}$E (ml min^{-1}) = 146 × kg + 482; $r = 0.92$ (fig. 2) with a mean value (±1 SD) of 202 ± 34 ml min^{-1} kg^{-1}. Tidal volume (VT) was related to weight according to the regression equation: VT (ml) = 7.3 kg + 25.6; $r = 0.91$, and the mean value (±1 SD) was 10.2 ± 1.7 ml kg^{-1}.

To keep $P\text{I}_{CO_2} < 0.5$ kPa, FGF (litre min^{-1}) settings during initial measurements ranged from 1.8 to 4.9 times $\dot{V}$E, with a mean value (±1 SD) of 3.0 ± 0.9 times $\dot{V}$E. The range of maximal inspired carbon dioxide tensions ($P\text{I}_{CO_2}$) varied from 0.10 to 0.57 kPa and end-tidal carbon dioxide tensions were between 4.0 and 5.0 kPa. At lower FGF, $P\text{I}_{CO_2}$ increased (fig. 3) and $P\text{E}'_{CO_2}$ tensions greater than 5 kPa occurred (fig. 4).

Neither $P\text{I}_{CO_2}$ nor $P\text{E}'_{CO_2}$ altered when I:E ratios were changed from 1:2 to 1:1 (table III, fig. 5).

DISCUSSION

When high fresh gas flows were used in this study, an end-tidal carbon dioxide tension of about 4.5 kPa was achieved at an average minute ventilation of 200 ml min^{-1} kg^{-1} at tidal volumes of 10 ml kg^{-1} and with ventilatory rates of 20 cycles per minute. These volumes are in agreement with those previously found during artificial ventilation in anaesthetized children (Okmian, Wallgren and Wahlin, 1966; Lindahl, Okmian and Thomson, 1979; Hulse, Lindahl and Hatch, 1984). Minute ventilation was maintained at this value throughout the study so that minimal fresh gas flow requirements could be assessed in relation to the way in which most clinical anaesthetists set their ventilation.

In T-piece systems used for mechanical ventilation, low fresh gas flows may cause alveolar rebreathing and increases in end-tidal carbon dioxide tension. The multiple of the estimated $\dot{V}\text{E}$ that should be used in order to avoid rebreathing is often debated (Nightingale, Richards and Glass, 1965; Rayburn and Graves, 1978; Rose and Froese, 1979). In the present study, FGF : $\dot{V}\text{E}$ ratios had to be set greater than 1.8 (range 1.8–4.9) to fulfill the prerequisites of $P\text{E}'_{CO_2}$ at about 4.5 kPa with a maximal inspired carbon dioxide tension below 0.5 kPa. $P\text{E}'_{CO_2}$ was, however, at the same value with an FGF of 1.8 as with an FGF of 4.9 times $\dot{V}\text{E}$. Thus, FGF of 1.8 to 2 times $\dot{V}\text{E}$ was high enough to avoid alveolar rebreathing in this study (fig. 4). However, when an FGF : $\dot{V}\text{E}$ ratio of 1.5 was used, some alveolar rebreathing occurred as $P\text{E}'_{CO_2}$ (mean values) increased from 4.5 to 5.1 kPa. Since, in children with normal lungs, the arterial end-tidal carbon dioxide tension difference is small (Lindahl, Yates and Hatch, 1987), these settings should produce Pa_{CO_2} values well within the normal range, despite the small amount of alveolar rebreathing. Alveolar rebreathing increased, however, even more when FGF was reduced to the actual $\dot{V}\text{E}$, as indicated by a further increase in $P\text{E}'_{CO_2}$ (fig. 4). This amount of alveolar rebreathing is probably unacceptably high. It was, however, uninfluenced by the change in I : E ratio from 1 : 2 to 1 : 1 (fig. 5). The unchanged $P\text{E}'_{CO_2}$ at FGF : $\dot{V}\text{E}$ ratios greater than 1.8 indicated that alveolar rebreathing was no longer present and that the carbon dioxide found in the inspired gas at these settings stayed in the apparatus and patient deadspaces—that is, the exchange of carbon dioxide over the alveolar membrane was unaffected by the presence of carbon dioxide in the inspired gas. For children with healthy lungs weighing between 3 and 20 kg, FGF set at $1.5 \times \dot{V}\text{E}$, calculated from the regression equation $\dot{V}\text{E}$ (ml min^{-1}) = 146 × kg + 482 found in this study, resulted in acceptable airway pressures of about 1.8 kPa and a $P\text{E}'_{CO_2}$ around 5 kPa. A recommendation of an FGF setting at 1.5 (146 × kg + 482) may, however, be difficult to memorize. If the expression is approximated to 200 × kg + 1000 it may be easier to remember, and comparisons of FGF calculated from the actually measured formula with that calculated from the approximated expression showed almost identical values (table IV).

Froese and Rose (1982) recommended FGF (ml min^{-1}) of (100 × kg + 1000) to obtain a Pa_{CO_2} of 4.9 and of (100 × kg + 1600) to obtain a Pa_{CO_2} of 4.0 kPa during controlled ventilation in children weighing 10–30 kg, but they suggested a minimum FGF of 3 litre min^{-1}. Since the FGF obtained using their formula does not reach 3 litre min^{-1} until 20 kg, it implies that all children weighing less than 20 kg should have an FGF of 3 litre min^{-1}. Our recommended formula of FGF (ml min^{-1}) = 200 × kg + 1000 gives an FGF value of 3 litre min^{-1} in a child of 10 kg, which is identical to the Froese and Rose recommendation at this weight. In children with weights between 10 and 20 kg, however, our recommended FGF settings are higher. In a 20-kg child, for example, we recommend an FGF of 5 litre min^{-1}, while the Froese and Rose formula still produces an FGF of 3 litre min^{-1} (fig. 6) for a Pa_{CO_2} of about 4.9 kPa, which is 15 % less than the actual $\dot{V}\text{E}$ found in this study at 20 kg (fig. 7) and would result in significant alveolar rebreathing (figs 3, 4). Froese and Rose (1982) (fig. 7), however, recommended the use of a greater minute ventilation (1.5 × FGF)

TABLE IV. *Comparison of fresh gas flow settings at various body weights when calculated from the measured formula 1.5 (146 × kg + 482) and from the approximated expression 200 × kg + 1000*

Body weight (kg)	Fresh gas flow settings (ml min^{-1})	
	1.5 (146 × kg + 482)	200 × kg + 1000
3	1380	1600
7	2260	2400
10	2910	3000
15	4010	4000
20	5100	5000

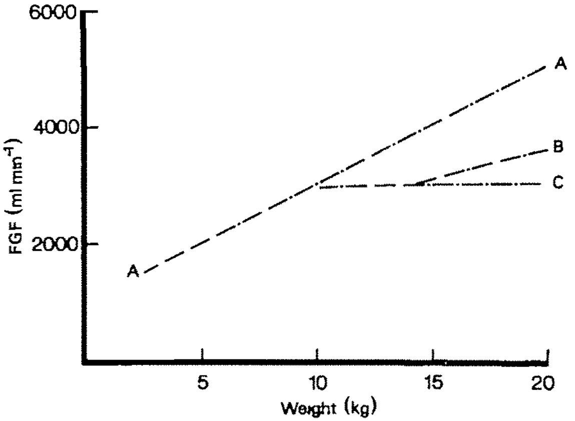

FIG. 6. Recommended fresh gas flow (FGF) settings. A From this study: FGF (ml min^{-1}) = 200 × kg + 1000. B From Froese and Rose (1982): FGF (ml min^{-1}) = 100 × kg + 1600 to achieve a Pa_{CO_2} of 4.0 kPa. Froese and Rose recommended a minimum FGF of 3 litre min^{-1}, which is also shown (C). (Their formula of 100 × kg + 1000 to achieve a Pa_{CO_2} of 4.9 kPa does not reach 3 litre min^{-1} until the weight is 20 kg.)

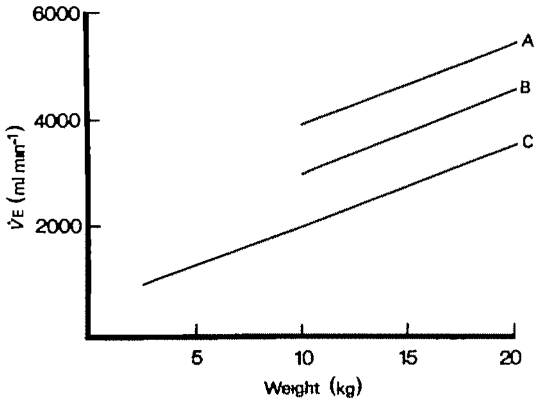

FIG. 7. Recommendations of preset minute ventilations ($\dot{V}_E$): A from: $\dot{V}_E$ (ml min^{-1}) = 1.5 (100 × kg + 1600) to obtain a Pa_{CO_2} of 4.0 kPa. B in the report of Froese and Rose (1982) from: $\dot{V}_E$ (ml min^{-1}) = 1.5 (100 × kg + 1000) to obtain a Pa_{CO_2} of 4.9 kPa and C in this study from the regression equation $\dot{V}_E$ (ml min^{-1}) = 146 kg + 482.

(fig. 7), than was used in this study, to obtain an arterial carbon dioxide tension of 4.9 kPa. The use of higher $\dot{V}_E$ as suggested by Froese and Rose must increase airway and mean intrathoracic pressure, which may decrease cardiac output (Cournand et al., 1948; Morgan et al., 1966) and could also increase the risk of barotrauma (Ovenfors, 1964). The ventilatory settings used in this study resulted in reasonably safe airway pressures and are, therefore, suggested even if this requires somewhat higher gas flows.

For children weighing less than 10 kg, our recommended formula would allow FGF below 3 litre min^{-1} to be used. For example, in a 3-kg infant, FGF of about 1.5 litre min^{-1} should be adequate, which is in agreement with the recommendations of an FGF set at $0.8 \times \sqrt{\text{weight}}$ (kg) suggested by Nightingale in 1982. However, it must be remembered that flowmeters are less accurate at these low settings, so inspired oxygen concentration should be monitored. Furthermore, Nightingale and Lambert (1978) showed considerable variation in carbon dioxide production in infants weighing less than 10 kg, making gas exchange unpredictable, so that if these low flows are used it is probably wise also to monitor end-tidal carbon dioxide.

In summary, we found that alveolar rebreathing during mechanically controlled ventilation with partial rebreathing systems in anaesthetized children weighing between 3 and 20 kg increased at FGF:$\dot{V}_E$ ratios less than 1.8 as indicated by increased inspired and end-tidal carbon dioxide tensions. At FGF settings greater than 1.5 times the actual $\dot{V}_E$, the degree of alveolar rebreathing was small enough to ensure normocapnoea. We conclude that, using minute volumes similar to those found in clinical practice (airway pressures of around 1.8 kPa), for children with healthy lungs a minimum FGF (ml min^{-1}) of 200 × kg + 1000 should be used to control ventilation with the T-piece in order to produce normocapnoea and minimize alveolar rebreathing.

ACKNOWLEDGEMENT

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PHARMACOKINETICS OF I.V. AND RECTAL METHOHEXITONE IN CHILDREN

S. BJÖRKMAN, J. GABRIELSSON, H. QUAYNOR AND M. CORBEY

SUMMARY

The pharmacokinetics of methohexitone were investigated in 15 healthy children undergoing minor surgery under inhalation anaesthesia. Six received 1% methohexitone 1–2 mg kg^{-1} i.v. and nine received 10% methohexitone 20–25 mg kg^{-1} per rectum. On i.v. administration, three-compartment pharmacokinetics generally applied. The mean elimination half-life of methohexitone was 193±75 min; that is, considerably longer than previously reported for children, but in good agreement with findings in adults. The mean clearance was 17.9±8.3 ml min^{-1} kg^{-1}, the volume of distribution at steady state was 2.1±0.24 litre kg^{-1} and the mean residence time was 134±47 min. The pharmacokinetic model used for the i.v. data was easily modified to suit the plasma concentration curves obtained on rectal administration. The mean bioavailability of methohexitone administered per rectum was 17%, with a six-fold variation between individuals.

Methohexitone has proved useful for the induction of anaesthesia when administered rectally in children (Budd, Dornette and Wright, 1965; Orallo and Eather, 1965; Goresky and Steward, 1979; Liu, Goudsouzian and Liu, 1980; Kraus and Taeger, 1982; Kuehn et al., 1983; Kraus et al., 1984; Liu et al., 1985; Quaynor, Corbey and Björkman, 1985). I.m. administration of methohexitone is possible, but confers no advantage over the other modes of administration (Kraus et al., 1984).

The pharmacokinetics of methohexitone in adults on i.v. administration, and in children on i.v., i.m. and rectal administration, have been described previously. In adults, two compartment kinetics were originally proposed (Brand et al., 1963; Breimer, 1976). With blood sampling for 6 h after the administration, a mean terminal methohexitone half-life of 1.6 h was found (Breimer, 1976). With blood sampling for 12 or 9 h, a third phase could often be discerned in the plasma concentration curves (Hudson, Stanski and Burch, 1983; Ghoneim et al., 1985). As a result, a considerably longer mean terminal half-life (3.9 h) was established.

In the only pharmacokinetic study on i.v. or i.m. methohexitone in children (Kraus et al., 1984), blood sampling was stopped after 2 h or less, and a two-compartment model was characterized. The mean methohexitone half-life was 36 min. The observation periods were also restricted to 135 min or less in all studies on methohexitone administered per rectum (Kraus and Taeger, 1982; Kuehn et al., 1983; Kraus et al., 1984; Liu et al., 1985; Engelhardt et al., 1986; Jantzen et al., 1986), with the exception of our study. In general, interest in these studies focused on the peak plasma concentrations obtained, and very few pharmacokinetic calculations could be performed. With a 4-h observation period, however, we were able to estimate an apparent mean half-life of 1.7 h from our plasma concentration curves (Quaynor, Corbey and Björkman, 1985).

In the light of the cited findings, we felt that a "terminal" methohexitone half-life of 36 min in children might be a serious underestimation and that the effects of the drug might be more protracted than this value would suggest. Therefore, we have re-evaluated the i.v. and rectal pharmacokinetics of methohexitone. The studies were performed on children undergoing routine

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SVEN BJÖRKMAN, B.PHARM., PH.D., Hospital Pharmacy, Malmö allmanna sjukhus, S-214 01 Malmö, Sweden. JOHAN GABRIELSSON, B. PHARM., PH.D., Department of Biopharmaceutics and Pharmacokinetics, Box 580, BMC, S-751 23 Uppsala, Sweden. HENRY QUAYNOR, M.D.; MARTIN CORBEY, M.D., B.S., F.F.A.R.C.S.; Department of Anaesthesia, Kongsbergs sykehus, N-3600 Kongsberg, Norway. Accepted for Publication: May 27, 1987.

surgery under inhalation anaesthesia. The plasma concentration data from the i.v. study and those from our previous rectal study were evaluated by means of a novel computer program, MAXFIT (Hakman and Gabrielsson, 1983), which estimates the time–concentration curve equation, area under the curve (AUC), clearance (*Cl*) and mean residence time (MRT) of a drug according to multi-exponential functions.

PATIENTS AND METHODS

Design of study

Fifteen healthy children, aged between 4 and 7 yr, who underwent minor, elective surgery, took part in the study. The weight and sex of each child are given in tables I and II. Informed consent was given by the children and their parents. Consent was also given by the Norwegian Medicines Control Authority. Rectal induction is the standard procedure in the department. I.v. induction was performed on six children who accepted the necessary extra venepuncture.

Premedication, consisting of morphine 0.15 mg kg^{-1}, hyoscine 0.01 mg kg^{-1} and diazepam 0.5 mg kg^{-1} (mixed in the same syringe) was given per rectum, 30–60 min before induction. A standard 6-cm rectal applicator, coated with 2% lignocaine gel, was used. No preceding cleansing enema was given.

For i.v. induction, a freshly prepared aqueous solution of 1% methohexitone sodium (Brietal) was used. A pre-determined dose, generally 1.5 mg kg^{-1}, was injected via an arm vein (contralateral to the one from which blood samples were taken) over 5 s. For rectal induction, a 10% solution was used. The dose was, generally, 25 mg kg^{-1}; however, a maximum dose of 500 mg was never exceeded. After induction, the patient was moved onto the operating table, and anaesthesia maintained with either halothane (children nos II–VI, 2, 7 and 8) or enflurane (children nos I, 1,

TABLE I. *Pharmacokinetic values associated with i.v. methohexitone in six children. The dose is here given as free acid. One milligram of the sodium salt corresponds to 0.92 mg of free acid. nd = not determined*

Patient No. (Sex)	Weight (kg)	Dose (mg kg^{-1})	$T_{\frac{1}{2}}^{\alpha}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	$T_{\frac{1}{2}}^{\gamma}$ (min)	*Cl* (ml min^{-1})	*Cl* (ml min^{-1} kg^{-1})	V^{ss} (litre)	V^{ss} (litre kg^{-1})	MRT (min)	AUC (mg min $litre^{-1}$)	AUC/dose (min kg $litre^{-1}$)
I(M)	13	0.92	0.8	24	301	196	15.1	29.4	2.26	150	61	66.3
II(M)	20	1.4	2.5	29	169	269	13.5	38.2	1.91	142	103	74.3
III(M)	15	1.4	4.6	25	nd	nd	nd	nd	nd	nd	nd	nd
IV(M)	20	1.4	3.7	19	231	261	13.1	47.0	2.35	180	106	76.4
V(M)	22	1.5	0.3	25	105	717	32.6	39.4	1.79	55	46	30.7
VI(F)	22	1.8	nd	13	161	333	15.1	48.0	2.18	144	122	66.1
Mean	18.7	1.40	2.4	23	193		17.9		2.10	134		62.9
SD	3.77	0.28	1.8	5.6	75		8.3		0.24	47		18.5

TABLE II. *Pharmacokinetic values associated with methohexitone administered per rectum in nine children. *As free acid, see legend to table I. †Tri-exponential function; ‡bi-exponential function. §Not included in calculation of the mean. nd = not determined*

Patient No. (Sex)	Weight (kg)	Dose* (mg kg^{-1})	K_a (min^{-1})	$T_{\frac{1}{2}}^{a}$ (min)	$T_{\frac{1}{2}}^{\beta}$ (min)	$T_{\frac{1}{2}}^{\gamma}$ (min)	AUC (mg min $litre^{-1}$)	AUC/dose (min kg $litre^{-1}$)
1(F)†	25	18	0.222	3.1	27	165	274	14.9
2(F)†	15	23	0.139	5.0	5	112	63	2.7
3(F)†	22	21	0.560	1.2	14	91	154	7.3
4(M)†	21	22	nd	nd	11	110	264	12.0
5(F)†	22	21	nd	nd	14	124	136	6.4
6(F)†	16	23	0.121	5.7	22	173	243	10.5
7(F)†	21	22	0.189	3.7	26	274	247	11.2
8(M)‡	21	19	0.077	9.0	(58)§		267	13.8
9(M)‡	14	19	nd	nd	(65)§		288	14.6
Mean	19.6	20.9	0.218	4.6	17	150	215	10.4
SD	3.7	1.8	0.175	2.7	8.1	62	78	4.2

3–6, 9) and nitrous oxide in oxygen ($F\text{I}_{\text{O}_2}$ 0.3). Further proceedings during and after the operation were described in our previous study (Quaynor, Corbey and Björkman, 1985).

A peripheral vein was cannulated before induction. Approximately 3 ml of blood was withdrawn before and 2, 4, 6, 10, 20, 30, 40 min and 1, 2, 3 and 4 h after the i.v. injection (from patients V and VI, samples were also taken at 5 and 6 h). After rectal administration blood samples were taken at 2, 5, 10, 15, 20, 25, 30, 40, 50, 60, 70 and 80 min and at 2, 3 and 4 h. After centrifugation, the plasma was frozen at −20 °C until analysis. The concentration of methohexitone in the plasma was determined by high performance liquid chromatography (Björkman and Idvall, 1984). The coefficient of variation of this method is 3–4% for methohexitone concentrations down to 62 ng mg^{-1}. The absolute limit of detection is approximately 10-fold lower.

Pharmacokinetic analysis

The pharmacokinetic values were calculated by the fitting of a tri-exponential or a bi-exponential function to the experimental i.v. and rectal time–concentration data. The program used, MAXFIT, is based on the theory of extended least squares (Hakman and Gabrielsson, 1983). Several runs using different initial estimates of the pharmacokinetic parameters were performed for each patient in order to avoid bias in those calculated. In the final fit, the observed data were weighted according to 1/variance of the experimental data. The goodness of fit of computed to experimental data was evaluated by analysis of the residuals. In most cases, this was done with both a tri-exponential and a bi-exponential function, and the one that gave the best fit (in terms of residual plots and least residual variance) was chosen.

The plasma concentration curve after an i.v. bolus injection can be described:

$$C_P = A.e^{-\alpha t} + B.e^{-\beta t} + C.e^{-\gamma . t} \qquad (1)$$

where C_P is the postinjection plasma concentration, A, B and C are the coefficients (concentration intercepts of the exponential terms at $t = 0$), α, β and γ are the rate constants, and t is the time after the injection.

The area under the plasma concentration curve (AUC), the total body clearance (Cl), the area under the first moment curve (AUMC) and the mean residence time (MRT) were calculated according to standard formulae (Gibaldi and Perrier, 1982). A re-arrangement of equation (1) according to (2) and (3) gave (4) (below), which was the function used in the actual calculations. Inclusion of a primary pharmacokinetic index, clearance, in the equation reduced the need for further computations and allowed the structure of the model to influence the curve-fitting process directly. In addition, confidence intervals or other estimates of variance were generated for the primary variables (Jusko, 1986).

$$\text{AUC} = \frac{A}{\alpha} + \frac{B}{\beta} + \frac{C}{\gamma} \qquad (2)$$

$$Cl = \frac{\text{Dose}}{\text{AUC}_{\text{i v.}}} \qquad (3)$$

$$C_P = \alpha\left(\frac{\text{Dose}}{Cl} - \frac{B}{\beta} - \frac{C}{\gamma}\right).e^{-\alpha t} + B.e^{-\beta . t} + C.e^{-\gamma . t} \qquad (4)$$

The volume of distribution at steady state, V^{ss}, was calculated according to Benet and Galeazzi (1979):

$$V^{ss} = Cl.\text{MRT} \qquad (5)$$

The contribution of the gamma phase in the time–concentration curve to the total $\text{AUC}_{\text{i v}}$ was calculated as:

$$\text{AUC}_\gamma = \frac{C}{\gamma} \qquad (6)$$

The rectal data were analysed in an analogous manner by means of equation (7):

$$C_P = -(A' + B').e^{-K_a . t} + A'.e^{-\beta t} + B'.e^{-\gamma . t} \qquad (7)$$

where K_a is the rate constant of absorption from the rectum, and A' and B' the coefficients, while β and γ in equation (7) will be comparable to β and γ in equation (1).

The areas under the curves (0–240 min) following rectal administration (AUC_r) were calculated by the linear trapezoidal rule, and the extrapolated area (240 min–infinity) was estimated by division of the last concentration value by γ.

Finally, the mean bioavailability (F) of methohexitone from the rectal administration was estimated as:

$$F = \frac{\text{mean}\left(\frac{\text{AUC}_r}{\text{dose}_r}\right)}{\text{mean}\left(\frac{\text{AUC}_{\text{i.v}}}{\text{dose}_{\text{i v}}}\right)} \qquad (8)$$

RESULTS

I.v. administration

Plasma methohexitone concentrations decreased generally in a tri-exponential manner

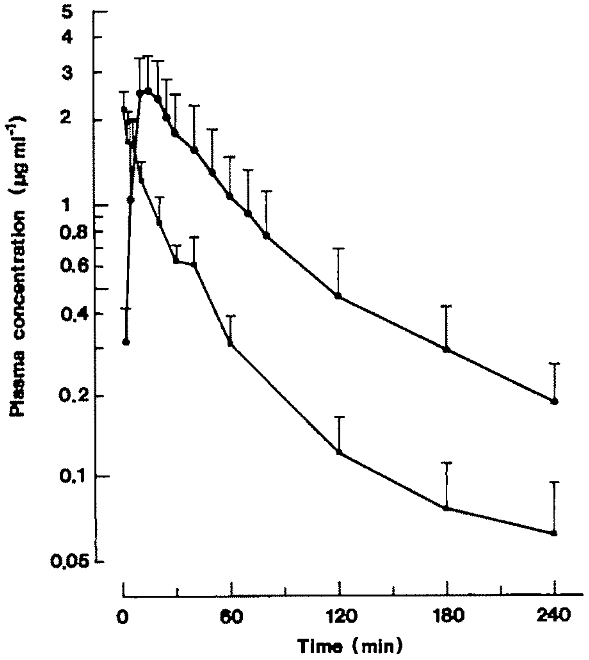

FIG. 1. The mean plasma concentration curves of methohexitone after rectal (upper curve) or i.v. (lower curve) administration. In order to permit calculations of means, the plasma concentrations found on i.v. administration in patients I, V and VI have been corrected for dose by multiplications by 1.5, 0.94 and 0.75, respectively. The bars mark the standard deviation in each point. Because of difficulties in blood sampling before the onset of anaesthesia, the first three points in the rectal curve are based on two, five and six measurements only.

following i.v. bolus administration (figs 1 and 2). The calculated pharmacokinetic values are given in table I. Most individual curves were clearly triphasic, but in patients III and VI, the γ and α phases, respectively, were not sufficiently well defined by data points to permit calculation of the pertinent parameters. The γ phases began 1–3 h after injection and, on average, the area under the γ phase (C/γ) was 40 ± 12% (SD) of the total area under the curve. The α phase of the curves (A/α) contributed 7 ± 6% to the AUC and, as A/α^2, only 0.2 ± 0.2% to the AUMC. The uncertainty in the determinations of A and α did not, therefore, introduce any great error to the further calculations.

The induction of anaesthesia with i.v. methohexitone was generally not very successful. A dose of 1.5 mg kg^{-1} did not ensure a smooth induction of anaesthesia, and some children had hiccup, which can be considered a dose-limiting side-effect. Rectal administration was better (Quaynor, Corbey and Björkman, 1985).

Rectal administration

The mean plasma concentration curve after rectal administration is depicted in figure 1 and the calculated pharmacokinetic parameters are presented in table II. For patients 1–7, the best fit to the data points was by a tri-exponential function, while a bi-exponential fit was more appropriate in patients 8 and 9. The absorption of methohexitone from the rectal lumen was very rapid, with an estimated mean half-life of 4.6 ± 2.7 min.

Comparison

There was no significant difference in weight between the patients in the two groups ($P > 0.7$, two-tailed Student's t test), and there was a complete overlap in ages. The groups were, therefore, regarded as weight- and age-matched. The mean half-life (β) of methohexitone was 23 ± 5.6 min on i.v. administration and 17 ± 8.1 min on rectal administration ($P > 0.2$), while the half-life (γ) was 193 ± 75 min after i.v. and 150 ± 62 min after rectal administration ($P > 0.4$). The absolute bioavailability of rectal methohexitone, as estimated from group means, was 17%. The bioavailability in each individual could not be calculated, but after rectal administration there was a nearly six-fold variation in AUC/dose (2.7–14.9 min kg litre^{-1}). After i.v. administration, the variation was approximately 2.5-fold (30.7–76.4 min kg litre^{-1}).

DISCUSSION

Pharmacokinetic studies in children are hampered by the limited number of blood samples that can be drawn for analysis. Possibly for this reason, five of the seven studies dealing with the rectal administration of methohexitone in children, and cited in the introduction, deal only with the peak plasma concentrations. A pharmacokinetic analysis on i.v., i.m. and rectal methohexitone in children was presented by Kraus and co-workers (1984) but, with blood sampling for not more than 2 h, only the α and β phases of the methohexitone disposition (on i.v. administration) could be demonstrated. The mean half-lives of 2.4 min (α) and 23 min (β) found by us are in reasonable agreement with the 3.6 and 36 min found by these authors in four anaesthetized children (16–22 kg).

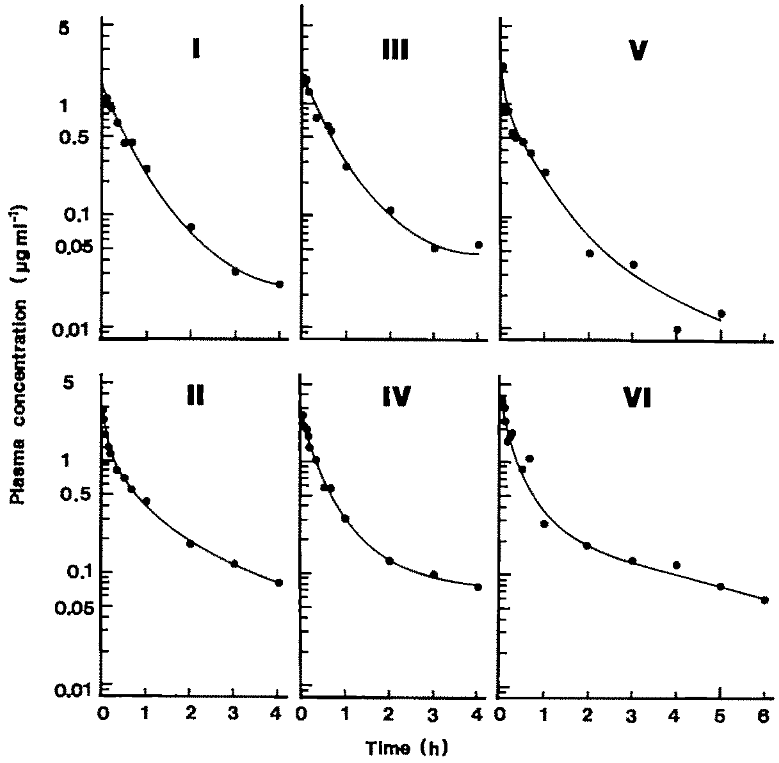

FIG. 2. Individual, computer-fitted plasma concentration curves of methohexitone after i.v. administration to six children. In patient V, the concentration at 6 h was below the limit of detection.

The values of clearance reported by Kraus and co-workers were somewhat greater (mean 422 ml min^{-1} or 22 ml min^{-1} kg^{-1}) than ours, possibly since missing the γ phase of a plasma concentration curve causes an underestimation of the AUC and a consequent overestimation of clearance. In spite of this, our data tend to confirm the conclusion of these authors, that methohexitone has a higher clearance (per kg body weight) in anaesthetized children than in similarly anaesthetized adults. For the latter category, mean clearance values of 10.9 and 8.7 ml min^{-1} kg^{-1} have been reported (Hudson, Stanski and Burch, 1983; Ghoneim et al., 1985). A comparison of methohexitone half-lives between children and adults is less straightforward, since these values depend on whether the plasma concentration data allow calculations according to bi-exponential or tri-exponential functions. The mean half-life of 193 min (3.2 h) found in our children is not, however, very different from that (3.9 h) found in young, anaesthetized surgical patients by Hudson, Stanski and Burch (1983) and by Ghoneim and co-workers (1985).

The finding that the terminal half-life of methohexitone in children is considerably longer than previously reported has clinical implications. Postoperative oversedation or respiratory depression is generally not a problem. The safety of rectal methohexitone was, however, challenged when a 6-year-old boy developed a suspected rebound of anaesthesia after a relatively high dose (Kaiser and Al-Rafai, 1985). The causal relationship of this to the induction with methohexitone has been questioned (Kretz and Eyrich, 1985). Nevertheless, the slow elimination of methohexitone emphasizes the need for adequate recovery facilities and postoperative surveillance of the patients.

The mean volume of distribution, $V^{ss} = 2.1$ litre kg^{-1}, was comparable to the V^{ss} values reported for adults: 2.2 litre kg^{-1} (Hudson, Stanski and Burch, 1983) and 1.2–2.0 litre kg^{-1} (Ghoneim et al., 1985). It is, however, considerably larger than the V^{ss} of 0.60–1.09 litre kg^{-1} found by Kraus and co-workers (1984).

The mean residence time of methohexitone in our children, 134±47 min (2.23±0.78 h), was shorter than in young anaesthetized adults (4.85 h) and in older, anaesthetized adults (5.00 h) (Ghoneim et al., 1985). This confirms the higher clearance in children, since the MRT is inversely proportional to *Cl* (Gibaldi and Perrier, 1982).

The pharmacokinetic studies of methohexitone in children have been performed in patients who also received inhalation anaesthesia for minor surgery. Volatile anaesthetics reduce hepatic blood flow (Batchelder and Cooperman, 1975) and inhibit drug-metabolizing liver enzymes (Takahashi, Shigematsu and Furukawa, 1974; Aune et al., 1983). This should, theoretically, affect the elimination of a drug that is cleared predominantly by oxidative metabolism, such as methohexitone. In adults, however, enflurane–nitrous oxide anaesthesia did not influence the clearance of methohexitone, although trends towards a larger volume of distribution and a longer half-life were found (Ghoneim et al., 1985). The influence of halothane–nitrous oxide anaesthesia has not been studied. However, halothane and enflurane interacted identically with hepatic microsomal cytochrome P450 *in vitro* (Takahashi, Shigematsu and Furukawa, 1974) and caused the same inhibition of antipyrine oxidation in rat hepatocytes (Aune et al., 1983). Also, enflurane, halothane and trifluoroacetic acid (a halothane metabolite) displaced phenytoin from serum proteins and changed the liver cytosol–serum binding distribution to a similar extent (Dale and Nilsen, 1986). Methohexitone and phenytoin are weakly acidic, lipophilic drugs with some structural similarities. It is, therefore, probable that if enflurane does not influence the pharmacokinetics of methohexitone, halothane will not do so either. This probable lack of influence is advantageous as far as pharmacokinetic studies are concerned, since volatile anaesthetics are administered for varying periods of time—depending on the duration of the operation. Complete standardization of anaesthetic management (as well as of surgical stress) can, therefore, never be achieved.

After rectal administration, the initial rapid distribution of methohexitone was not visible as a distinct phase in the plasma concentration curve, since it is masked by the increase in concentration resulting from uptake from the rectal lumen. The β and γ phases of the curves were, however, similar after the two modes of administration. In our previous paper (Quaynor, Corbey and Björkman, 1985), the half-life of methohexitone was estimated from a line drawn through the three last points of the plasma concentration curve. Calculation according to a tri-exponential function (patients 1–7) gave half-lives (γ) that were, on the average, 31% longer than previously estimated. Calculation according to a bi-exponential function (patients 8 and 9) gave, on the average, half-lives that were 25% shorter than those previously estimated.

The mean bioavailability of 17% is consistent with the figure reported by Kraus and co-workers. The large variation in rectal bioavailability does not seem to be of clinical significance, as long as the peak plasma concentration exceeds 2 mg $litre^{-1}$ (Liu et al., 1985; Quaynor, Corbey and Björkman, 1985). The hepatic extraction ratio of methohexitone has been reported to be 0.67 in normal adults (Richter et al., 1980). Since the hepatic blood (or plasma) flow in our children is not known, the hepatic extraction ratio cannot be calculated exactly. In view of the high extraction ratio in adults, it can, however, be assumed that the limited bioavailability is partly the result of an extensive first pass metabolism in the liver. Only from the lowest part of the rectum does the venous drainage bypass the liver (De Boer, De Leede and Breimer, 1984). Instillation of methohexitone solution to the rectum of a child positioned appropriately will most probably place the drug farther up the large bowel.

In conclusion, we have compared the pharmacokinetics of methohexitone after i.v. and rectal administration on age- and weight-matched children and shown that a pharmacokinetic model based on i.v. data can be applied to plasma concentration curves found on rectal administration. The terminal half-life of methohexitone was considerably longer than previously reported and did not seem to differ between children and adults. The comparatively slow elimination of methohexitone emphasizes the need for adequate recovery facilities and postoperative surveillance of the patients.

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ARTERIAL OXYGEN TENSIONS MEASURED CONTINUOUSLY IN PATIENTS BREATHING 21% OXYGEN AND NITROUS OXIDE OR AIR

K. SUGIOKA, R. W. CATTERMOLE AND P. S. SEBEL

SUMMARY

Changes in arterial oxygen tensions in nine anaesthetized patients during controlled ventilation with either 79% nitrous oxide in oxygen or air only, were measured continuously using an intra-arterial oxygen electrode. When the patients were ventilated with the mixture, there was a significant increase in Pa_{O_2} *of 2.74 ± 1.08 kPa* ($P < 0.002$) *over control values obtained while the subjects were awake and breathing air spontaneously. Changing the inspired gas from nitrous oxide in oxygen to air while ventilation was held constant resulted in a significant decrease in* Pa_{O_2} *of 2.22 ± 0.94 kPa* ($P < 0.001$). *However, these* Pa_{O_2} *values were not statistically significantly different from control values. We conclude that continuous accurate measurement of arterial oxygen tension is feasible provided that corrections are made in the electrode system for anaesthetic gases. We also found that the increase in* Pa_{O_2} *when 79% nitrous oxide in 21% oxygen was used, when compared with air, was lower than values proposed by previous investigators. The decrease in* Pa_{O_2} *when the inspired gas was changed back to room air was less than that found by others and there was no evidence of hypoxia when patients were ventilated on air alone after inspiring the mixture.*

Increases in PA_{O_2} and Pa_{O_2} during the uptake of 79% nitrous oxide in 21% oxygen, and their decrease during the elimination of this mixture while breathing room air has been observed by many investigators (Rackow, Salanitre and Frumin, 1961; Heller, Watson and Imredy, 1967; Frumin and Edelist, 1969; Shah et al., 1971). However, except for the work of Heller, Watson and Imredy (1967), who used an intra-arterial oxygen electrode in dogs, to our knowledge there have been no studies of changes in arterial oxygen tensions measured continuously in man breathing 79% nitrous oxide in 21% oxygen or room air. In this study Pa_{O_2} was continuously recorded in anaesthetized patients using an oxygen electrode of new design in order to assess the variations in Pa_{O_2} when changing from nitrous oxide in oxygen to air and back again.

PATIENTS, MATERIALS AND METHODS

This study was approved by the ethics committee of The London Hospital. In order to measure Pa_{O_2} accurately and continuously in the presence of nitrous oxide, an intra-vascular oxygen electrode (Kontron Medical) developed by Eberhard, Fehlman and Mindt (1979) was used (fig. 1). Compared with random arterial blood-gas analyses using a blood-gas analyser (ABL2 Radiometer), the electrode demonstrated an accuracy resulting in a correlation coefficient of 0.99 (fig. 2). In addition to accuracy, the sensor had to meet the following requirements: sterility; small diameter; adequate response time; freedom from fibrin deposition; insensibility to high nitrous oxide concentrations.

The first requirement was met by using gamma sterilization, the second was fulfilled by using an electrode 0.55 mm in diameter which permitted continuous concurrent pulsatile arterial pressure measurements and intermittent blood sampling when inserted through a 20-gauge intra-arterial cannula. The third requirement was met by a

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KENNETH SUGIOKA, M.D., F.F.A.R.C.S., Department of Anesthesiology, Duke University Medical Center, Durham, North Carolina, U.S.A. 27710. ROGER W. CATTERMOLE, M.B., B.CH., F.F.A.R.C.S.; PETER S. SEBEL, PH.D., F.F.A.R.C.S.I.; The Anaesthetic Unit, The London Hospital Medical College, Whitechapel, London. Accepted for Publication: November 28, 1985.

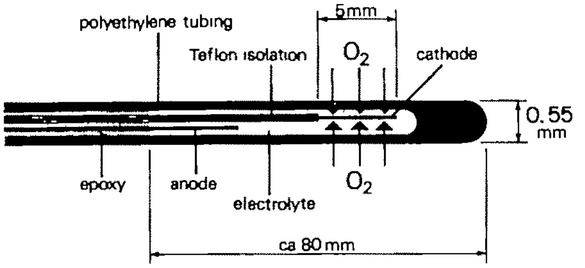

FIG. 1. Diagram of oxygen electrode. (By permission of Eberhard, Fehlman and Mindt (1979).)

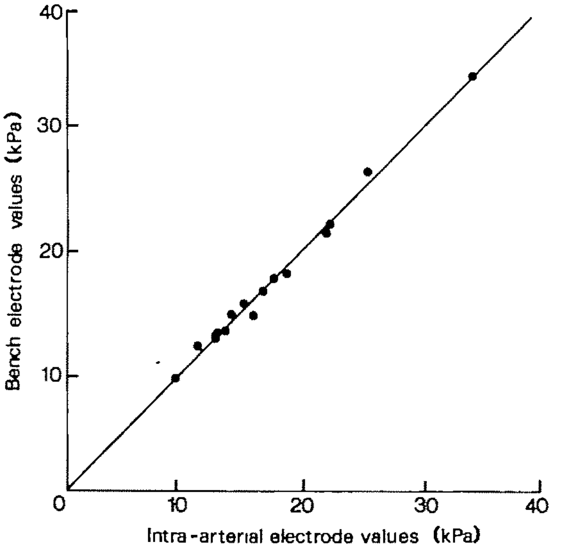

FIG. 2. Comparison of oxygen tensions. Pa_{O_2} values on ordinate from samples of arterial blood analysed on (ABL2 Radiometer) blood-gas analyser. Values on abscissa obtained from measurements by intra-arterial electrode. Correlation coefficient = 0.996; slope = 1.01.

response time of 30 s or less for 95 % of full scale changes. The fourth requirement was met by using sensors which had been pretreated with heparin. Those sensors which had not been pretreated with a heparin coating had a 20 % failure rate, probably as a result of fibrin deposition on the sensor over a period of hours; those sensors pretreated with heparin were left *in situ* for up to 8 h without change (±3 mm Hg) in output or response time. The fifth requirement was met by using an electrode with a silver cathode which, when polarized at 600 mV or less, was insensitive to nitrous oxide.

Having satisfied the requirements for instrumentation, the sensor was used in nine patients (four female) undergoing intra-cranial neurosurgical procedures. These patients were chosen because there would be no manipulation of the thorax or abdomen which could cause changes in the Pa_{O_2}. The age range was from 17 to 75 yr.

Following control measurement of Pa_{O_2} while the subject was breathing room air, anaesthesia was induced with thiopentone. Muscle paralysis was produced with tubocurarine and tracheal intubation was performed. The lungs were ventilated using a Brompton Manley ventilator with enflurane and nitrous oxide in oxygen mixtures. Fentanyl was given i.v. Halothane was not used because of its adverse effect on the accuracy of oxygen electrodes. The end-tidal carbon dioxide concentration was measured continuously with an infra-red carbon dioxide analyser and the ventilator was adjusted such that $P\text{E}_{CO_2}$ was maintained between 4.65 and 5.32 kPa. Arterial pressure was monitored continuously. $F\text{I}_{O_2}$ was monitored by a fuel cell which was calibrated on room air and 100 % oxygen. After the sensor was inserted it was calibrated *in vivo* against multiple blood-gas samples obtained while the patient was on low or zero concentrations of nitrous oxide.

After being ventilated with nitrous oxide in oxygen ($F\text{I}_{O_2} = 0.4$) for at least 30 min to ensure complete nitrogen washout, the patients' lungs were ventilated with 79 % nitrous oxide and 21 % oxygen and, after 20 min, the breathing mixture was changed to room air supplied via an air compressor. After 10 min on room air the inspired gas was again changed to the 79:21 mixture. In some patients this manoeuvre of changing from the mixture to air and back was repeated several times with at least 10 min between nitrous oxide in oxygen and air breathing to ensure adequate nitrogen washout. At the end of these observations the patients' lungs were ventilated with 60 % nitrous oxide in 40 % oxygen until the end of the surgical procedure. Data are presented as mean (±SD). Statistical analysis was with Student's paired *t* test.

RESULTS

The mean control value of Pa_{O_2} obtained from all subjects while they were awake and breathing air was 11.0±1.89 kPa. The lowest Pa_{O_2} was in a 75-yr-old man who had a control value of 9.0 kPa and who developed bronchospasm during anaesthesia. The highest control Pa_{O_2} was in a 17-yr-old man who was hyperventilating involuntarily when the sample was drawn. His Pa_{O_2} was 14.1 kPa and his Pa_{CO_2} 4.0 kPa.

TABLE I. Pa_{O_2} *values (kPa): control, after ventilation of the patients' lungs with 79% nitrous oxide in 21% oxygen for 20 min; after ventilation with air for 10 min; after return to ventilation with the gas mixture*

Patient No.	Control (kPa)	After 79% N_2O–21% O_2 for 20 min (kPa)	After air for 10 min (kPa)	After return to N_2O–O_2 (kPa)
1	12.8	19.8	15.5	20.8
		20.5	15.5	—
2	9.3	11.8	10.6	12.0
		10.8	9.2	12.8
		10.9	10.2	11.4
3	9.7	12.6	11.2	12.6
4	12.2	15.8	12.6	14.0
5	12.6	16.0	13.6	16.0
		16.2	13.0	—
		16.8	14.1	—
6	9.0	10.2	8.5	11.0
		11.8	8.5	9.4
		9.4	8.3	9.8
7	14.1	15.4	13.4	16.0
		16.0	12.2	16.4
		14.9	12.8	16.0
		15.6	12.8	15.2
		14.6	12.9	14.6
		14.6	12.9	14.6
		15.6	12.8	15.4
		14.8	12.2	14.4
8	10.2	11.4	10.4	12.0
9	9.4	10.9	10.0	11.4
Mean	11.0	14.1	12.0	13.8
SD	1.89	2.95	2.27	2.77

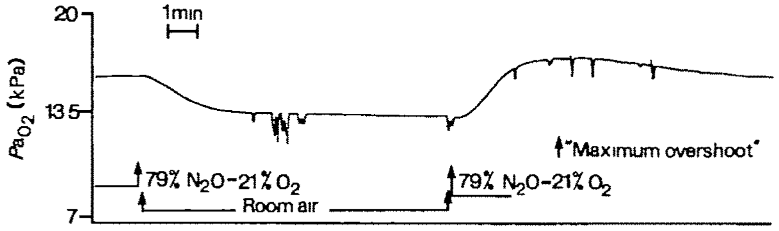

FIG. 3. Recording of Pa_{O_2} using intra-arterial electrode while changing inspired gases from a mixture of 79% nitrous oxide–21% oxygen to air and back to the mixture. Artefacts from electrocautery included to demonstrate electrode stability.

The increase in Pa_{O_2} over the mean control values when patients were ventilated for 20 min with 79% nitrous oxide in 21% oxygen as the inspired gas was 2.74 ± 1.88 kPa ($P < 0.002$). The mean steady state value with this gas mixture was 14.1 ± 2.95 kPa. There was a significant decrease ($P < 0.001$) in Pa_{O_2} to a mean of 12.0 ± 2.27 kPa when the patients' lungs were ventilated for 10 min with air without changing any other conditions. The mean decrease amounted to 2.22 ± 0.94 kPa. In only the two patients discussed above did the Pa_{O_2} at this point decrease below control values. However, there was no significant difference ($P < 0.1$) between mean control values and the mean Pa_{O_2} at this point in the study.

When the patients were again ventilated with 79% nitrous oxide in 21% oxygen, the Pa_{O_2} increased significantly ($P < 0.001$) to a mean

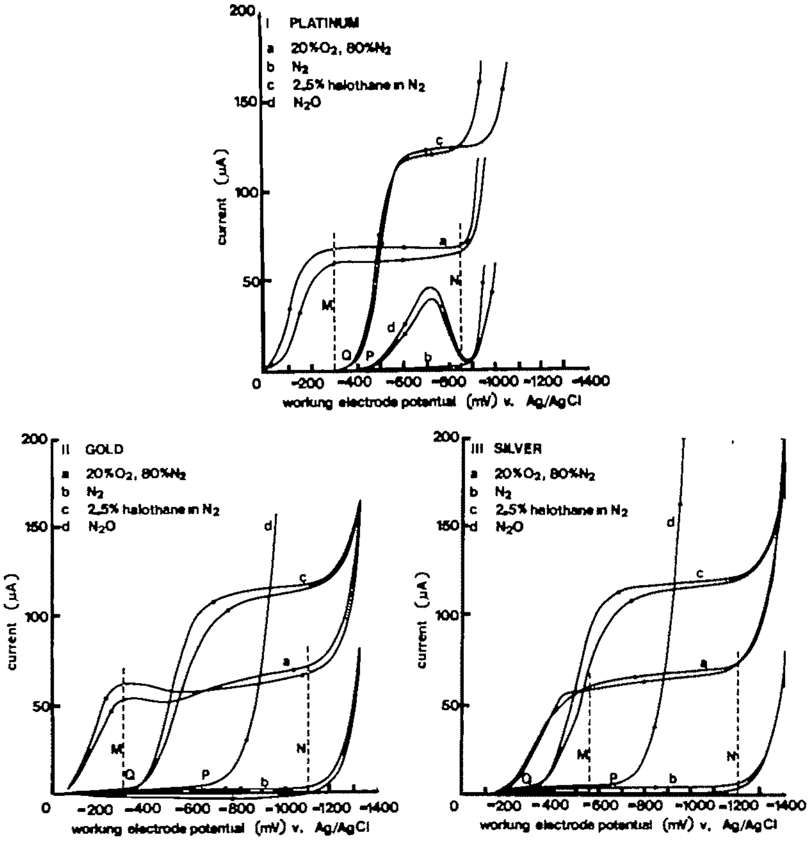

FIG. 4. Polarograms obtained using platinum cathode I, gold cathode II, and silver cathode III in aqueous solutions containing dissolved nitrous oxide–oxygen, nitrogen, halothane–nitrogen, and nitrous oxide. (By permission of Eberhard and Mindt (1978).)

value of 13.8 ± 2.77 kPa. The mean increase amounted to 2.21 ± 0.96 kPa. The values obtained from this study are shown in table I. A recording of the cycles of events which took place during a study is given in figure 3. The artefacts were caused by cautery and were included to demonstrate the rapid return of the electrode output to precautery values.

An "overshoot" of Pa_{O_2} was seen in most patients upon resumption of ventilation with 79% nitrous oxide in 21% oxygen after ventilation with air. This is shown in the recording. However, there was no significant difference ($P < 0.22$) between the values obtained while ventilating with the mixture before and after ventilation with air. At no time were significant changes seen in arterial pressure, ECG, heart rate or end-tidal carbon dioxide concentration.

DISCUSSION

The oxygen electrode used in this study was polarized at 600 mV or less and the cathode material was silver. This was done to ensure relative insensibility to the high concentrations of nitrous oxide used in this study. Figure 4 (Eberhard and Mindt, 1979) shows polarograms which demonstrate the sensitivity of most oxygen electrodes to nitrous oxide and this can cause errors up to 30% above true oxygen tension (Evans and Cameron, 1978). This problem has been studied extensively (Hahn et al., 1979, 1981).

It is noted here that, in so far as can be determined, none of the electrodes used to measure arterial oxygen tensions in previous studies of this kind, was corrected for the error caused by the presence of nitrous oxide in the inspired gas mixture.

The improved technology in oxygen sensors has made it possible to measure Pa_{O_2} accurately and continuously in man during the uptake and elimination of nitrous oxide. The ease of its use permits ungloved but sterile insertion intravascularly through any 20-gauge cannula without disturbing the measurement of other items usually measured by intravascular means, thus enhancing its usefulness.

Farhi and Olszowka (1968) constructed a mathematical model using end-expired oxygen (PA_{O_2}) as the unit of measurement to analyse the uptake and elimination of nitrous oxide as a soluble inert gas. Based on their calculations, it was predicted that the "average" alveolus would show a Po_2 increase of 6.5 kPa when the inspired gas was changed from air to 78% nitrous oxide in 22% oxygen. They predicted also that, upon changing back to air, the Po_2 would decrease initially by 2.66 kPa. They reasoned that the above increase in Po_2, along with a 0.27-kPa increase in Pa_{CO_2}, would occur as a result of the "concentration" effect of nitrous oxide resulting from the rapid absorption of this gas from the alveolus. This would result in diminished alveolar volume with subsequent increases in the pressures of oxygen and carbon dioxide. They also reasoned that the initial decrease in Po_2 during the elimination of nitrous oxide by breathing air would be less than the increase, because of the buffering effect of nitrogen entering the alveoli and countering the "dilution" effect of nitrous oxide as it diffused back into the alveoli. In addition, they felt that the haemoglobin would release more oxygen as it reached the steep part of the dissociation curve and that this oxygen would also diffuse back into the plasma to help counter the "dilution" effect.

Since the publication of the above data several workers have investigated changes in Po_2 during the uptake and elimination of nitrous oxide by using various techniques. Frumin and Edelist (1969) found that, in patients breathing 79% nitrous oxide in 21% oxygen spontaneously, arterial oxygen tensions decreased minimally when the inspired gas was changed to air (a maximum decrease of 1.2 kPa in one patient out of nine after 3 min on air). Shah and colleagues (1971) used eight volunteers in a sitting position breathing 79% nitrous oxide in 21% oxygen and found that the mean increase in PA_{O_2} after 80 s was 4.0 kPa (less than the 6.5 kPa predicted by Farhi and Olszowka (1968)). They stated that the Pa_{O_2} increased after nitrous oxide in oxygen, but gave no figures for the mean increase and concluded that the lesser increase in Pa_{O_2} as compared with PA_{O_2} was the result of an increase in alveolar–arterial difference.

In a study using a mathematical lung model and three subjects, Scrimshire and Tomlin (1973) predicted the increase in PA_{O_2} after 16 breaths of 79% nitrous oxide in 21% oxygen would be 4.39 kPa if the lungs were inflated at a constant volume. They predicted that the decrease in PA_{O_2} upon changing to air would be 2.66 kPa initially and implied that the reason for the difference between the increase and decrease in PA_{O_2} was the rapid nitrogen wash-in upon changing to room air.

In reviewing our data which are based on arterial oxygen tensions, we found that the mean increase of 2.74 ± 1.88 kPa with 79% nitrous oxide in 21% oxygen as the inspired gas was less than the predicted increase in Pa_{O_2} suggested by both Farhi and Oszowka (1968) and Scrimshire and Tomlin (1973). This difference may be accounted for by the fact that these previous studies measured changes in alveolar oxygen tension using end-tidal oxygen, whereas, in this study, continuous arterial oxygen tensions were measured. We found that the mean decrease of 2.22 ± 0.94 kPa in Pa_{O_2} when the inspired gas was changed to air was close to that predicted by the above authors. The outstanding point of difference between their data and ours was that the increase in Pa_{O_2} after breathing 79% nitrous oxide in 21% oxygen was much less than they predicted for the increase in Pa_{O_2}. We believe that the lesser increase in Pa_{O_2} was a reflection of an increase in alveolar–arterial difference. Our findings are at variance with those of Scrimshire and Tomlin (1973), who predicted a decrease in alveolar–arterial difference when nitrous oxide in oxygen was the inspired gas. However, because our patients were anaesthetized and in a supine or prone position, an increase in shunt would be more likely than in "awake" volunteers or mathematical models. Alternatively, a reduction in functional residual capacity on changing from the awake to the anaesthetized state could account for these differences.

Although there was no significant difference between the Pa_{O_2} values found while breathing 79% nitrous oxide in 21% oxygen before and after air breathing, in most patients there was a definite "overshoot" as high as 1.33 kPa upon resumption of breathing nitrous oxide in oxygen. After 2–3 min in all patients the Pa_{O_2} decreased to the mean values listed. The probable explanation of this overshoot is the very rapid absorption of the soluble nitrous oxide during the first 2–3 min, with a consequent increase in Pa_{O_2} as the result of the rapid shrinkage of the alveoli. The return to the mean values of Pa_{O_2} after the initial increase can be explained on a steady state basis wherein the blood concentration of nitrous oxide reaches a value at which the net exchange of nitrous oxide across the alveoli is negligible and there is stabilization of alveolar volume. Another possible explanation of the overshoot could be that areas with low ventilation:perfusion ratios receive more soluble gas (for example nitrous oxide) when the mixture is changed from room air to nitrous oxide. The ventilation:perfusion ratio in these areas will become higher temporarily.

The fact that there was no significant difference in mean Pa_{O_2} between awake control values and while being ventilated with air during anaesthesia, would indicate that the patients were not hypoxic at any time.

The following conclusions can be drawn from this study:

(1) It is now feasible clinically to use an intravascular oxygen sensor when one is needed.

(2) "Diffusion hypoxia" does not exist if patients have an adequate cardiorespiratory system and there are no changes in respiratory volume when changing from nitrous oxide in oxygen to air (hypoxia being defined as Pa_{O_2} during air breathing which decreases significantly below baseline values.)

(3) Unless high oxygen tensions are needed, the use of high concentrations of nitrous oxide (up to 79%) results in more than adequate oxygenation in patients with normal cardiorespiratory systems. This finding may be helpful in anaesthetizing patients when hyperoxia might be harmful. It might also be possible to use lower concentrations of supplementary anaesthetic agents. This does not negate the probable desirability of using higher oxygen concentrations at the end of anaesthesia or when the cardiorespiratory system is likely to be depressed.

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Br. J. Anaesth. (1987), 59, 1554–1556

NEUROLEPTIC MALIGNANT SYNDROME AND MALIGNANT HYPERTHERMIA

In Vitro *Comparison with Halothane and Caffeine Contracture Tests*

R. KRIVOSIC-HORBER, P. ADNET, E. GUEVART, D. THEUNYNCK AND P. LESTAVEL

SUMMARY

The in vitro *halothane and caffeine contracture tests have been performed on muscle tissue from six survivors of the neuroleptic malignant syndrome. The results, which are expressed in accordance with the criteria of the European MH Group, defined five of the subjects as MHN and one patient as MHE. It is concluded that there is no common pathophysiological link between the neuroleptic malignant syndrome and malignant hyperthermia.*

The neuroleptic malignant syndrome (NMS) is an uncommon but dangerous complication of treatment with neuroleptic drugs. First described by Delay and Deniker in 1968, the syndrome is characterized by hyperthermia, muscle rigidity, altered consciousness and autonomic disturbances during neuroleptic treatment. The pathogenesis of the syndrome is unknown. Central dopamine receptor blockade has been implicated both in the pathogenesis of neuroleptic malignant syndrome (Henderson and Wooten, 1981) and in its therapy (Mueller, Vester and Fermaglich, 1983). A primary defect in skeletal muscle has been suggested in view of similarities in the clinical presentations of neuroleptic malignant syndrome and anaesthetic-induced malignant hyperthermia (Andersson, 1972; Tollefson, 1982; Caroff, Rosenberg and Gerber, 1983; Downey, Rosenberg and Caroff, 1984). These similarities, including successful treatment with dantrolene (Delacour et al., 1981), suggest a common pathophysiology underlying both disorders.

In malignant hyperthermia, survivors of the crisis and susceptible family members can be identified by the increased sensitivity of muscle fibres to contracture induced by both caffeine and halothane (Britt et al., 1973; Ellis, Harriman and Currie, 1978). These *in vitro* contracture tests are, at present, the most reliable method of identifying individuals susceptible to malignant hyperthermia. The aim of this study was to define if a relationship exists between neuroleptic malignant syndrome and malignant hyperthermia susceptibility, by using the halothane and the caffeine contracture tests on survivors of the neuroleptic malignant syndrome.

PATIENTS AND METHODS

Six survivors of the neuroleptic malignant syndrome were investigated; their clinical histories are summarized in table I. All patients had received neuroleptic drugs before the crisis. Body core hyperthermia in the absence of underlying infection was greater than 38.5 °C. Physical examination revealed neurological disorders, including akinesia, muscle rigidity, autonomic dysfunction and fluctuating level of consciousness. The creatinekinase concentration was always increased and reflected rhabdomyolysis. Acute myoglobinuric renal failure occurred in three patients.

If the patient had received dantrolene sodium, a period of 48 h was allowed to elapse after

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R. KRIVOSIC-HORBER, M.D., P. ADNET, M.D., E. GUEVART, M.D., D. THEUNYNCK, M.D. (Département d'Anesthésie Réanimation Chirurgicale 1); P. LESTAVEL, M.D. (Service de Réanimation Polyvalente); Hôpital B, Centre Hospitalier Régional Universitaire, 59037 Lille Cedex, France. Accepted for Publication: June 4, 1987.

TABLE I. *Characteristics of the patients studied. CK = Creatine kinase concentration*

Patient no.	Sex	Age (yr)	(Psychotic illness/ others)	Neuroleptic agent	Clinical features	CK(iu litre^{-1})	Dantrolene sodium
I	F	37	Schizophrenia	Levomepromazine	Hyperthermia (39 °C) Rigidity Fluctuating consciousness	12000	600 mg day^{-1} by mouth
II	F	40	Psychosis	Levomepromazine	Hyperthermia Rigidity Stupor Renal failure	25000	1 mg kg^{-1} day^{-1} i.v.
III	M	54	Psychosis	Levomepromazine Trifluoperazine Trihexyphenidyle	Hyperthermia (39.9 °C) Akinesia Stupor Renal failure	18000	No
IV	M	73	Burn	Thiapride Haloperidol Trihexyphenidyle	Hyperthermia (38.5 °C)	10000	No
V	M	40	Alcoholism Delirium tremens	Droperidol	Hyperthermia (39 °C) Rigidity Autonomic dysfunction Stupor Renal failure	56000	600 mg day^{-1} by mouth
VI	F	58	Melancholia	Levomepromazine	Hyperthermia (39 °C)	11500	200 mg day^{-1} by mouth

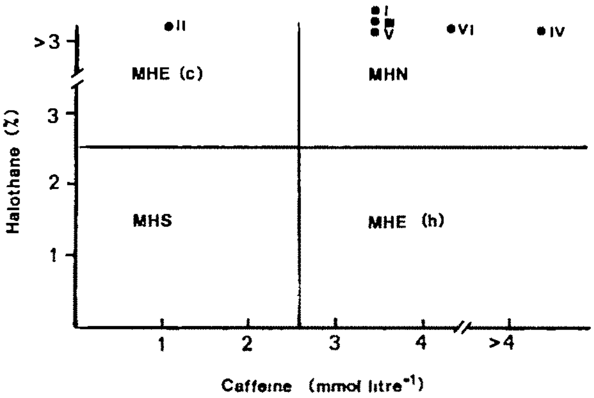

FIG. 1. Diagnostic criteria. MHS implies a threshold (an increase in tension ⩾ 0.2 g) at 2% or less halothane and at 2 mmol litre^{-1} or less caffeine. MHN implies no threshold at 2% or less halothane and 2 mmol litre^{-1} or less caffeine. MHE implies a threshold to either halothane or caffeine at the above mentioned concentrations.

discontinuing the infusion of the drug before performing the contracture tests.

According to the European protocol (Ellis et al., 1984), the *in vitro* test involved measuring the tension developed by muscle strips exposed to increasing concentrations of caffeine and halothane in a muscle bath containing Krebs–Ringer solution. The test was performed at 37 °C and the tissue bath was gassed with 5% carbon dioxide in oxygen. The biopsy was stimulated electrically at a frequency of 0.2 Hz to produce mechanical twitches, thus demonstrating viability.

RESULTS

The results (fig. 1) expressed in accordance with the criteria of the European group defined five of the subjects as MHN (malignant hyperthermia negative). The muscle from patient II developed a contracture of 0.4 g tension on exposure to caffeine 1 mmol litre^{-1}; there was no contracture on exposure to halothane. This subject was defined as MHE (malignant hyperthermia equivocal to caffeine).

DISCUSSION

In malignant hyperthermia, a genetic defect in the sarcoplasmic reticulum accounts for a loss of control of intracellular ionized calcium in the presence of triggering agents, resulting in an increase in intracellular calcium concentration, muscle contracture, metabolic stimulation and changes in permeability. This is reflected in the lower concentrations of caffeine and halothane required to produce contractures *in vitro* in muscle biopsy specimens from susceptible patients. This provides the basis of a screening test which we have been using in our laboratory. The fact that none of the patients in our study was MHS suggests that there is no pharmacological abnormality in neuroleptic malignant syndrome similar to that found in malignant hyperthermia.

Few results of investigations using halothane and caffeine contracture tests in survivors of the neuroleptic malignant syndrome are to be found in the literature. Caroff, Rosenberg and Gerber (1983) and Downey, Rosenberg and Caroff (1984) studied contractility of muscles in a patient with neuroleptic malignant syndrome and found a contracture of 5.1 g tension on exposure to 1.2% halothane—a response diagnostic, for those authors, of susceptibility to malignant hyperthermia. Denborough, Collins and Hopkinson (1985) reported the results of an *in vitro* test in a patient with neuroleptic malignant syndrome. The 1%-halothane contracture was 0.45 g and the caffeine 2-mmol litre^{-1} contracture 0.4 g. The patient's brother also had positive contracture responses. Tollefson (1982) studied contractility of muscles in a patient with neuroleptic malignant syndrome. The tests were negative for both halothane and caffeine, and Tollefson concluded that there was no common peripheral pathophysiological link between neuroleptic malignant syndrome and malignant hyperthermia. It is possible that some of the variations in the results in different centres could be attributed to variations in laboratory procedures.

In the present study, the absence of pharmacological abnormalities in the muscle of patients susceptible to neuroleptic malignant syndrome, and the laboratory differences between neuroleptic malignant syndrome and malignant hyperthermia, suggest that factors other than a muscle defect may be more important for most patients with neuroleptic malignant syndrome.

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EFFECTS OF ADENYLATE CYCLASE ACTIVATORS ON PORCINE SKELETAL MUSCLE IN MALIGNANT HYPERPYREXIA

A. T. R. SIM, M. D. WHITE AND M. A. DENBOROUGH

Malignant hyperpyrexia (MH) is an often fatal complication of general anaesthesia, which is attributed to a dysfunction of skeletal muscle (Denborough, 1980). While the precise site of the abnormality associated with MH remains unknown (Gronert, 1980), it is thought that an increase in myoplasmic Ca^{2+} concentration can account for most of the features of MH (Denborough, 1980). The concentration of Ca^{2+} in the myoplasm is regulated by the sarcoplasmic reticulum (SR), and the enzyme adenylate cyclase has been found to influence SR Ca^{2+}-transport in cardiac muscle (Kirchberger and Tada, 1976) and slow skeletal muscle (Schwartz et al., 1976). Furthermore, halothane, which precipitates an MH episode (Gronert, 1980) and induces MH-susceptible (MHS) skeletal muscle to contract *in vitro* (Ellis et al., 1971), activates the adenylate cyclase system (Sprague, Yang and Ngai, 1974). Consequently, this link between adenylate cyclase and MH has been investigated. Although increased concentrations of cyclic AMP (cAMP), and increases in adenylate cyclase activity, have been reported in MHS human muscle (Willner, Cerri and Wood, 1981; Ellis et al., 1984), no difference has been found between control and MHS porcine skeletal muscle, in relation to adenylate cyclase activity (Ono, Topel and Althen, 1976, 1977). Since MHS skeletal muscle characteristically contracts in response to various reagents *in vitro* (Moulds and Denborough, 1974a), we have investigated the effect of adenylate cyclase activation on the contractility of control, and MHS porcine, skeletal muscle *in vitro.*

SUMMARY

The effect of adenylate cyclase activation on the in vitro *contractures of control and malignant hyperpyrexia susceptible (MHS) porcine muscle was investigated. While fluoride and molybdate ions potentiated drug-induced contractures in control muscle, other activators of adenylate cyclase (forskolin and noradrenaline) did not. Furthermore, fluoride and molybdate had no effect on MHS skeletal muscle contractility. Cyclic AMP content, basal adenylate cyclase activity and molybdate-stimulated adenylate cyclase activity of MHS skeletal muscle was not significantly different from that of control muscle. It is concluded that increased activity of adenylate cyclase does not represent the primary skeletal muscle defect which predisposes to porcine MH.*

MATERIALS AND METHODS

Pigs susceptible to MH were bred from crosses of MHS Landrace and Large White breeds. Animals used as controls were either commercially purchased, unrelated animals or MH-negative siblings of MHS pigs.

Susceptibility to MH was assessed by the *in vitro* contracture testing of skeletal muscle, according to Okumura, Crocker and Denborough (1979).

Anaesthesia and surgical procedures were carried out using the method of Okumura, Crocker and Denborough (1979), except that the neurolept agent Stresnil (4-fluor-4-(4-(2-pyridyl)-1-piperazinyl)-butyrophenone) was used for premedication.

For pharmacological studies, the method described by Moulds and Denborough (1974b) was used. Muscle preparations which did not produce

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A. T. R. SIM, PH.D.; M. D. WHITE, PH.D.; M. A. DENBOROUGH, M.D., D.PHIL., D.SC., F.R.C.P., F.R.A.C.P.; Department of Medicine and Clinical Science, The John Curtin School of Medical Research, The Australian National University, Canberra, ACT, 2600, Australia. Accepted for Publication: July 28, 1987.

Correspondence to M.A.D.

TABLE I. *The effect of adenylate cyclase activators on drug-induced contractures in porcine control skeletal muscle. Control muscle fibres were pretreated for 5 min with the appropriate adenylate cyclase activator and then exposed to the appropriate diagnostic reagent. Results are expressed as the mean contractures (g) ± SEM. For comparisons between pre-treatment and no pre-treatment:* $^{*}P < 0.05$ $^{**}P < 0.01$; $^{***}P < 0.001$ *(Student's paired* t *test)*

	Pretreatment				
Diagnostic reagent	None	Sodium molybdate 20 mmol litre^{-1}	Sodium fluoride 20 mmol litre^{-1}	Forskolin 100 µmol litre^{-1}	Noradrenaline 100 µmol litre^{-1}
3% Halothane	0.01 ± 0.005	0.37 ± 0.07	0.29 ± 0.13	0.01 ± 0.01	0.0
	(n = 21)	(n = 21)***	(n = 19)*	(n = 6)	(n = 4)
Caffeine	0.02 ± 0.01	0.28 ± 0.06	0.13 ± 0.04	0.0	0.005 ± 0.005
2 mmol litre^{-1}	(n = 16)	(n = 16)***	(n = 17)**	(n = 5)	(n = 7)
Suxamethonium	0.01 ± 0.005	0.09 ± 0.02	0.13 ± 0.05	—	0.01 ± 0.01
1 mmol litre^{-1}	(n = 19)	(n = 19)***	(n = 12)*		(n = 6)
Potassium chloride	0.02 ± 0.01	0.24 ± 0.12	—	—	—
80 mmol litre^{-1}	(n = 8)	(n = 8)			

a twitch response equivalent to a tension of 0.75 g or more, were rejected.

Drugs and chemicals were added directly into the organ bath at the final concentrations indicated in the text. Forskolin (Calbiochem) and dantrolene sodium (Norwich Eaton) were dissolved in dimethyl sulphoxide, final concentrations of which in the organ bath did not exceed 0.4% (v/v) and had no effect on muscle integrity. When used, thymol-free halothane was administered by passing carbogen through a Dragewick halothane vaporizer.

Adenylate cyclase activity was determined by measuring the change in cAMP content of skeletal muscle homogenates in the presence of ATP and a phosphodiesterase inhibitor. Samples of muscle were obtained at biopsy, frozen immediately in liquid nitrogen and stored at −70 °C until required. No sample was stored for more than 4 weeks, and control and MHS samples of equivalent storage age were assayed at the same time, in each study. Using a mortar and pestle, cooled to −70 °C, approximately 0.5 g of muscle sample was ground to a fine powder and homogenized in 20 volumes of homogenization buffer using a Polytron at maximum setting for 2 × 10-s intervals. The homogenization buffer contained EDTA 4 mmol litre^{-1}, potassium chloride 150 mmol litre^{-1}, Tris-HCl 10 mmol litre^{-1}, pH 7.4. Aliquots (50 µl) of muscle homogenate were added to 50 µl of assay buffer at 0 °C. The assay buffer contained ATP 1 mmol litre^{-1}, creatine phosphate 20 mmol litre^{-1} and creatine phosphokinase 100 u ml^{-1}, theophylline 20 mmol litre^{-1}, magnesium chloride 50 mmol litre^{-1}, Tris-HCl 50 mmol litre^{-1}, pH 7.4. The reaction was started by transferring the samples to a 37 °C water bath. After 10 min, the reaction was stopped by the addition of 5% TCA 150 µl (w/v) and the protein precipitated by centrifugation at 2000 *g* for 15 min. The supernatant was collected, extracted with water-saturated ether and assayed for cAMP content using a competitive-binding assay kit (Amersham Radiochemicals). Experiments were performed in duplicate. Dose–response curves for different chemicals were carried out on muscle from one animal.

All adenylate cyclase activators used did not interfere with the cAMP assay. Adenylate cyclase activity was expressed as the amount of cAMP formed per mg of protein per min.

Protein estimations were carried out using the method of Peterson (1977).

RESULTS

Pharmacological action of adenylate cyclase activators on skeletal muscle

The results obtained when control porcine skeletal muscle fibres were pretreated with adenylate cyclase activators and then exposed to 3% halothone, caffeine 2 mmol litre^{-1}, suxamethonium 1 mmol (Anectine, Burroughs Wellcome) or potassium chloride 80 mmol litre^{-1} are shown in table I. These activators, alone, did not stimulate contractures in control or MHS skeletal muscle. Pre-treatment with 20 mmol litre^{-1} of fluoride or molybdate significantly

TABLE II. *Effect of adenylate cyclase activators on drug-induced contractures in MHS porcine skeletal muscle fibres. MHS muscle fibres were pretreated for 5 min with the appropriate adenylate cyclase activator and then exposed to the appropriate diagnostic reagent. Results are expressed as the mean contractures (g) ± S.E.M. There was no significant difference between contractures in the absence or presence of any adenylate cyclase activators*

	Pretreatment				
Diagnostic reagent	None	Sodium molybdate 20 mmol litre^{-1}	Sodium fluoride 20 mmol litre^{-1}	Forskolin 100 µmol litre^{-1}	Noradrenaline 100 µmol litre^{-1}
3% Halothane	0.85 ± 0.1 (n = 14)	0.91 ± 0.1 (n = 14)	0.59 ± 0.13 (n = 14)	0.95 ± 0.21 (n = 5)	1.35 ± 0.19 (n = 5)
Caffeine 2 mmol litre^{-1}	0.51 ± 0.07 (n = 11)	0.38 ± 0.08 (n = 11)	0.31 ± 0.08 (n = 7)	0.96 ± 0.27 (n = 5)	0.71 ± 0.19 (n = 5)
Suxamethonium 1 mmol litre^{-1}	0.42 ± 0.04 (n = 8)	0.42 ± 0.06 (n = 8)	0.29 ± 0.11 (n = 7)	—	0.23 ± 0.19 (n = 5)
Potassium chloride 80 mmol litre^{-1}	2.04 ± 0.43 (n = 8)	1.86 ± 0.46 (n = 8)	—	—	—

TABLE III. *Effect of dantrolene on fluoride- and molybdate-potentiated contractures in control porcine skeletal muscle. Control muscle fibres were pre-treated with sodium fluoride 20 mol litre^{-1} or molybdate 20 mmol litre^{-1} for 5 min followed by dantrolene sodium 6 µmol litre^{-1} for a further 5 min and then exposed to halothane or caffeine.* ***P < *0.001 for comparison between contractures in the abscence and presence of dantrolene (Student's paired* t *test)*

	Pretreatment				
Diagnostic reagent	None	Molybdate only	Molybdate + dantrolene	Fluoride only	Fluoride + dantrolene
3% Halothane	0.01 ± 0.005 (n = 21)	0.43 ± 0.11 (n = 5)	0.017 ± 0.016 (n = 5)***	0.38 ± 0.11 (n = 5)	0.05 ± 0.04 (n = 5)***
Caffeine 2 mmol litre^{-1}	0.02 ± 0.01 (n = 16)	0.29 ± 0.03 (n = 5)	0.012 ± 0.012 (n = 5)***	0.12 ± 0.03 (n = 5)	0.0 (n = 5)***

potentiated contractures in response to halothane, caffeine and suxamethonium (table I). Molybdate also increased the magnitude of the potassium chloride-induced contractures, but this was not statistically significant. Pretreatment with equivalent concentrations of sodium chloride in place of $NaF + Na_2MoO_4$ had no effect.

Lower concentrations of molybdate also significantly potentiated drug-induced contractures in control muscle. Using molybdate 10 mmol litre^{-1}, mean contractures of 0.26 ± 0.08 g ($n = 7$) were obtained in response to 3% halothane, while molybdate 2.5 mmol litre^{-1} produced a mean contracture of 0.125 ± 0.05 g ($n = 3$).

While fluoride and molybdate potentiated drug-induced contractures in control skeletal muscle, forskolin and noradrenaline (100 µmol litre^{-1}) did not (table I). Furthermore, noradrenaline up to 2 mmol litre^{-1} failed to potentiate drug-induced contractures (results not shown).

When these experiments were carried out with MHS porcine muscle, the results were different from those obtained with control muscle (table II). Fluoride and molybdate 20 mmol litre^{-1} produced no significant changes in drug-induced contractures. Forskolin and noradrenaline also failed to have any effect on contractures induced by the same drugs in MHS tissue (table II).

The effect of dantrolene on fluoride and molybdate-potentiated contractures was also examined (table III). Dantrolene was added to the organ bath after fluoride and molybdate and before the diagnostic reagent. Treatment of muscle fibres with dantrolene 6 µmol litre^{-1} prevented fluoride- and molybdate-potentiation of contractures in response to 3% halothane and caffeine 2 mmol litre^{-1} (table III). Dantrolene was equally effective in reversing fluoride- and molybdate-potentiated drug-induced contractures (not shown).

TABLE IV. *Adenylate cyclase activity of control and MHS porcine skeletal muscle. Where appropriate, sodium molybdate 20 mmol litre^{-1} with or without dantrolene 6 µmol litre^{-1} was included in the assay buffer. Results are expressed as the mean adenylate cyclase activity ± SEM. There was no significant difference between control and MHS samples*

	Adenylate cyclase activity (pmol cAMP/mg protein/min)		
Sample	None	Molybdate 20 mmol litre^{-1}	Molybdate 20 mmol litre^{-1} + dantrolene 6 µmol litre^{-1}
Control	6.79 ± 0.97 (n = 8)	30.17 ± 6.55 (n = 8)	24.08 ± 5.25 (n = 5)
MHS	8.06 ± 1.34 (n = 8)	28.12 ± 4.31 (n = 7)	25.23 ± 3.1 (n = 5)

Adenylate cyclase activity of control and MHS skeletal muscle

Cyclic-AMP content of control samples varied between 8.46 and 30 pmol/mg protein and between 12.8 and 41.3 pmol/mg protein for MHS samples. The mean cAMP content of MHS skeletal muscle homogenates (22.39 ± 3.7 pmol/mg protein) was not significantly different from that of control muscle (18.19 ± 2.49 pmol/mg protein). Furthermore, basal adenylate cyclase activity in MHS skeletal muscle homogenates was not significantly different from the basal adenylate cyclase activity of control samples (table IV).

The effect of adenylate cyclase activators on skeletal muscle adenylate cyclase activity was also studied. Dose–response curves showed that the inclusion of fluoride, molybdate, forskolin and noradrenaline in the assay buffer produced a concentration-dependent increase in adenylate cyclase activity in control samples (fig. 1). These agents were thus shown to activate adenylate cyclase in porcine skeletal muscle as they do in other tissues. However, there was no significant difference between control and MHS samples in relation to molybdate-stimulated adenylate cyclase activity (table IV). Furthermore, dantrolene had no significant effect on molybdate-stimulated adenylate cyclase activity in control or MHS samples (table IV).

DISCUSSION

Adenylate cyclase activity has been reported to be increased in MHS humans (Willner, Cerri and Wood, 1981; Ellis et al., 1984), but not in MHS pigs (Ono, Topel and Althen, 1976, 1977). While the results of these different investigations may reflect a real difference and species variability, it may be noted that the use of an animal model allows more stringent attention to the choice of controls, muscle type and experimental conditions. In the investigation of human MH, controls are obtained from various sources and may involve different muscle types (Willner, Cerri and Wood, 1981) and anaesthetic conditions (Gronert and Van Dyke, 1984). However, variations in the concentrations of circulating catecholamines (Halter, Pflug and Porter, 1977) and adenylate cyclase activity in different muscle types (Festoff, Oliver and Reddy, 1977) may lead to spurious differences between subjects. The animals used in the present study were subject to the same experimental conditions and results showed that there was no difference between control and MHS porcine muscle in relation to cAMP content and basal adenylate cyclase activity.

While fluoride and molybdate increased the sensitivity of control muscle to the diagnostic reagents, other activators of adenylate cyclase (forskolin and noradrenaline) did not. Fluoride has been shown to activate adenylate cyclase only in broken cell preparations (Perkins and Moore, 1971) while forskolin is a general activator of adenylate cyclase in all systems, including whole cell preparations (Seamon and Daly, 1981). Since the muscle preparations used in this study were essentially intact, it is unlikely that fluoride increased the sensitivity of control muscle through a direct action on adenylate cyclase. Furthermore, it is not known whether molybdate stimulates adenylate cyclase in whole cell preparations, but it is generally believed to have a mechanism of action similar to that of fluoride (Richards and Swislocki, 1979). Although fluoride and molybdate were both found to stimulate adenylate cyclase activity in skeletal muscle homogenates,

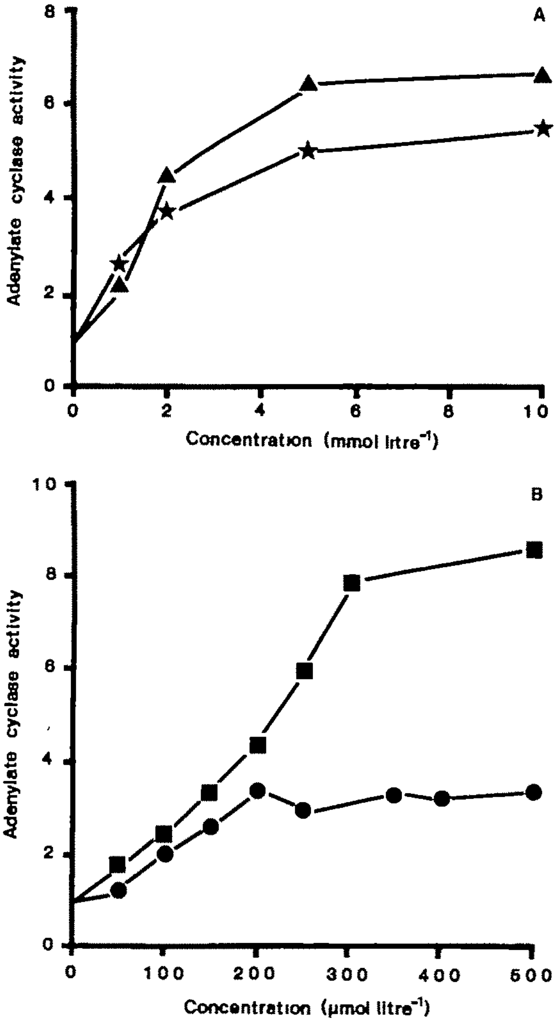

FIG. 1. Effect of adenylate cyclase activators on adenylate cyclase activity in control skeletal muscle. A: Sodium fluoride (▲) and sodium molybdate (★) were included in the assay buffer at the concentrations indicated (mmol litre^{-1}). B: Forskolin (■) and noradrenaline (●) were included in the assay buffer at the concentrations indicated (µmol litre^{-1}). Each point on the curves represents one individual experiment. Adenylate cyclase activity results are expressed as the ratio of stimulated: basal activity.

there was no significant difference between control and MHS muscle in relation to molybdate-stimulated adenylate cyclase activity. Furthermore, dantrolene, which antagonized and prevented fluoride- and molybdate-potentiation of drug-induced contractures, had no effect on molybdate-stimulated adenylate cyclase activity. For these reasons, it is unlikely that the pharmacological action of fluoride and molybdate is related to activation of adenylate cyclase activity. It is also concluded that the primary defect associated with MH does not reside in the adenylate cyclase system.

The finding that fluoride and molybdate did not increase the contractile response of MHS muscle suggests that MHS muscle has a decreased sensitivity to fluoride and molybdate. Both fluoride and molybdate are potent inhibitors of protein phosphatases (Hollander, 1971) and, as such, might interfere with the phosphorylation state of certain proteins involved in muscle contractility. Experiments to explore this hypothesis have been started.

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INTRATHECAL MIDAZOLAM IN THE RAT: EVIDENCE FOR SPINALLY-MEDIATED ANALGESIA

C. S. GOODCHILD AND J. M. SERRAO

SUMMARY

This study investigated the possible analgesic effect of midazolam as a result of interruption of those spinal cord pathways taken by pain afferents. Experiments were performed on 15 male Wistar rats with chronically implanted lumbar subarachnoid catheters. The threshold for pain induced by brief passage of electric current between pairs of electrodes placed on the tail and the skin of the neck was measured before and after subarachnoid injections of midazolam. Intrathecal midazolam caused a significant ($P < 0.02$) increase in the threshold for pain in the tail, but not in the neck; this response was not produced by intrathecal injections of vehicle and was blocked by prior intraperitoneal injections of the benzodiazepine antagonist RO 15–1788. We also performed experiments on frog sciatic nerves which showed that midazolam did not have a local anaesthetic action. We conclude that intrathecal midazolam causes spinally-mediated analgesia by binding to benzodiazepine receptors in the spinal cord.

It has been suggested that benzodiazepines might have analgesic properties via an action in the spinal cord. Rigoli (1983) reported that the extradural administration of midazolam to postoperative patients and individuals with chronic pain afforded significant analgesia. However, relatively large doses were used and significant sedation was produced, thus making the measurements of pain by analogue scores unreliable.

Benzodiazepine stereospecific binding sites have been demonstrated in the spinal cord (Mohler and Okada, 1977) and endogenous benzodiazepine-like substances have been discovered in human cerebrospinal fluid (CSF) (Deckert, Kuhn and Przuntek, 1984); however their role has not been identified as yet. Elsewhere in the central nervous system membrane preparations of benzodiazepine receptors have been linked with the receptors for gamma amino butyric acid (GABA) in the control of chloride channels (Schoch et al., 1985); opening of these channels on the surface membrane of a neurone produces hyperpolarization and, therefore, inhibition of firing. GABA has been implicated in spinal cord anti-nociceptive mechanisms (Game and Lodge, 1975), but interaction between benzodiazepine stereospecific binding sites in the spinal cord and GABA in anti-nociception has not been proven.

Whitwam and colleagues (1982) showed that lumbar intrathecal application of the water soluble imidazo benzodiazepine, midazolam, interrupted reflexes in renal sympathetic nerves evoked by electrical stimulation of mixed peripheral nerves at intensities sufficient to recruit group III and IV afferent fibres (*some* of which carry pain information); resting sympathetic nerve activity was *not* decreased and only the reflex from the hind leg (input to lumbar dorsal horn—the site of application of the drug) and not the foreleg (input to cervical dorsal horn) was attenuated. The observed effects were, therefore, likely to result from interruption of pathways in the lumbar dorsal horn, although a mild local anaesthetic effect affecting very fine nerves only could not be ruled out. The purpose of our investigation was to determine if the interruption of the afferent pathways taken by nociceptive afferents could afford spinally-mediated analgesia, and to define whether this effect was the result of a stereospecific interaction with benzodiazepine receptors, rather than a local anaesthetic effect.

C. S. GOODCHILD, M.A., M.B., B.CHIR., PH.D., F.F.A.R.C.S.; J. M. SERRAO, M.B., B.S., F.F.A.R.C.S.; Department of Anaesthesia, The University of Leeds, 24 Hyde Terrace, Leeds LS2 9LN.
Accepted for Publication: June 1, 1987.
Correspondence to C. S. G.

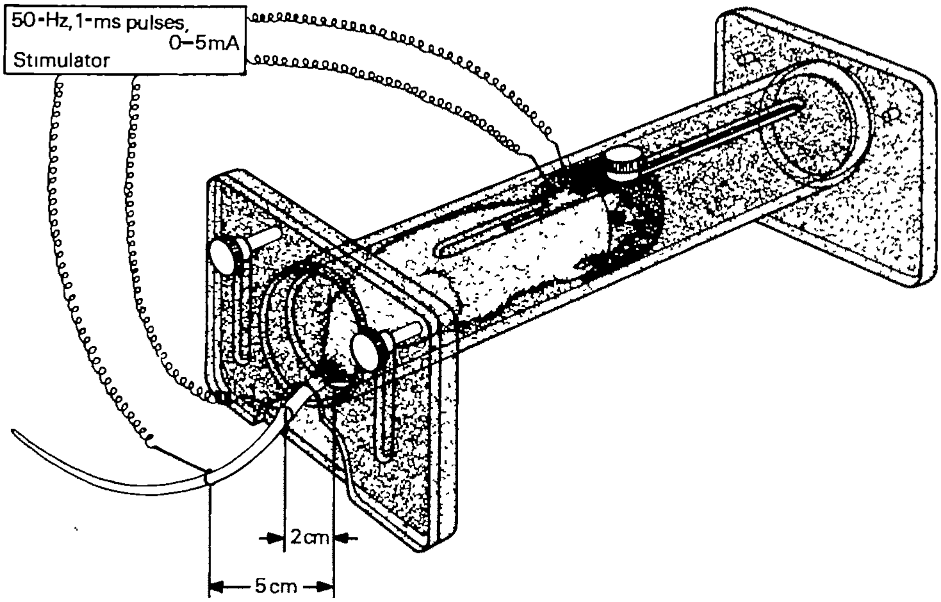

FIG. 1. Schematic representation of equipment used to measure current threshold for pain in the tail, and in the neck.

MATERIALS AND METHODS

Investigations in the rat

Catheter implantation. Fifteen male Wistar rats (150–250 g) were anaesthetized with 5% halothane in oxygen-enriched air. Anaesthesia was maintained with 1.75% halothane in oxygen-enriched air given by face mask, the animals being placed in the prone position. A lower lumbar laminectomy was performed and a Portex catheter (i.d. 0.25 mm, o.d. 0.75 mm) was introduced to the lumbar subarachnoid space as previously described (Bahar, Rosen and Vickers, 1984); the catheter was advanced in the subarachnoid space until the tip lay in the upper lumbar region. The catheter was tailor-made for each rat and the deadspace was measured using a Hamilton micro syringe after subcutaneous tunnelling to an exit wound at the back of the neck before the subarachnoid insertion of the catheter. The wound at the back of the neck, before the nylon (Ethilon) sutures and the animal allowed to recover from anaesthesia.

Soon after recovery (10–15 min) the catheter position was verified by the intrathecal injection of 2% plain lignocaine solution 10 μl followed by a volume of normal saline (the previously measured deadspace volume) to flush the catheter. The catheter was judged to be in the correct position if the hind limbs of the rat became paralysed and were dragged behind the animal within 20–30 s of the injection. The animals were then allowed a further period of 2–4 h to recover fully from the effects of the local and general anaesthetics, although they were moving around their cage, eating and drinking normally within 1 h of the surgical preparation.

Animals with a negative lignocaine test or with obvious neurological damage following laminectomy were excluded from the study at this stage and were killed under anaesthesia. Five animals were used for a study of possible effects of intrathecal injection of vehicle and 10 were used for a study of differential spinal analgesia. The subarachnoid position of catheters was confirmed histologically 1 month after implantation (fig. 2).

Intrathecal vehicle. Each rat was placed in a restrainer (fig. 1) and two stimulating electrodes were placed on the skin of the tail. These electrodes consisted of two wires wrapped around the tail which was moistened with electrode jelly; the negative wire was placed 2 cm from the base of the tail and the positive wire 5 cm distal to the negative. These were connected to a peripheral nerve stimulator (Digitimer DS 10) which delivered rectangular 1-ms pulses at a frequency of

50 Hz at a voltage up to 100 V. The current delivered through the electrodes was measured as a voltage decrease across a 1-kΩ resistor in series with the electrodes using a Gould digital storage oscilloscope. The minimum current necessary to produce an obvious reaction to pain (movement and vocalization) was measured every 10 min.

After 30 min, 25 µl of vehicle (normal saline) balanced to pH 3.5 with sodium hydroxide and hydrochloric acid injected through the intrathecal catheter and the deadspace (the volume of which was measured at the time of catheter insertion) was flushed with physiological saline. The minimum current necessary to produce pain was again measured in the skin of the tail every 10 min for 30 min. This was followed by an intrathecal injection of midazolam 25 µl (125 µg, flushed in with physiological saline) and the current threshold for pain measured for a further 30 min, as before. If the animals were released at this stage they behaved normally; that is, they were able to move around their cages, stand on their rear limbs, and feed and drink normally with no obvious signs of central nervous system depression. Finally, the catheter position was confirmed by another intrathecal injection of 2 % plain lignocaine solution, as above.

Differential analgesia. Each animal was placed in the restrainer as above. In addition to the pair of electrodes on the tail, two needle electrodes were also placed 1 cm apart in the loose skin of the neck. The minimum electrical current (50 Hz, 1 ms, 0–5 ma) necessary to produce signs of discomfort was measured for each of these pairs of electrodes every 5 min. After six control readings a 2-ml intraperitoneal (i.p.) injection of either physiological saline (five rats) or RO 15–1788 5 mg (five rats) was given through a hole in the side of the restrainer without removal of the animal; the operator performing the measurements of current thresholds of pain did not know whether the rat under investigation had received saline or benzodiazepine antagonist.

The current threshold for pain was measured as before every 5 min for a further 30 min before and after the intrathecal injection of midazolam 10 µl. Care was taken to inject only 10 µl of midazolam (50 µg) to the subarachnoid space, by injecting a precise volume down the catheter (10 µl plus catheter deadspace) at a rate of 1 $\mu l\ s^{-1}$, using a Hamilton microsyringe; thus knowing the precise volume of the catheter deadspace (measured at the time of the catheter insertion) allowed us to be certain that only 10 µl of midazolam solution emerged from the catheter tip into the subarachnoid space.

Finally, the catheter position was confirmed by another intrathecal injection of 2 % plain lignocaine solution, as above.

The mean current thresholds for pain in each 30-min period obtained with intrathecal vehicle and with differential analgesia were calculated and the results obtained after i.p. and intrathecal injections were normalized for each animal by dividing these values by the control values in each case. Student's *t* test for paired data was then applied to these data to compare thresholds before and after i.p. injections, and before and after intrathecal injections, of either vehicle or midazolam.

Investigations in the frog

Two adult frogs were stunned by a blow to the back of the head, and pithed. The sciatic nerves of each frog were dissected out from the spine to the knee. The distal portion of each nerve was placed on bipolar silver stimulating electrodes with the negative terminal proximal. The proximal portion of each nerve was placed on bipolar recording electrodes and the evoked potentials amplified (Gould Universal Amplifier) and displayed on a Digital storage oscilloscope; the captured waveforms were subsequently printed out on an ink jet recorder (Mingograf).

Supramaximal electrical stimuli were delivered to the nerve and, after control recordings had been obtained, the following solutions were placed in sequence in a pool on the nerve between the stimulating and recording electrodes: (a) vehicle: physiological saline with HCl and NaOH (pH of 3.5); (b) midazolam solution 0.5 ml (5 mg ml^{-1}); (c) 2 % plain lignocaine solution 0.5 ml.

RESULTS

Investigations in the rat

Histological. Histological examination of the spinal cords of some of the rats 4–6 weeks after the study confirmed the subarachnoid position of the catheter. Figure 2 shows a photomicrograph of a transverse section of rat spinal cord stained with haemotoxylin and eosin. Among the nerve roots in the subarachnoid space is a circular object which is arachnoid infiltration around a Portex catheter

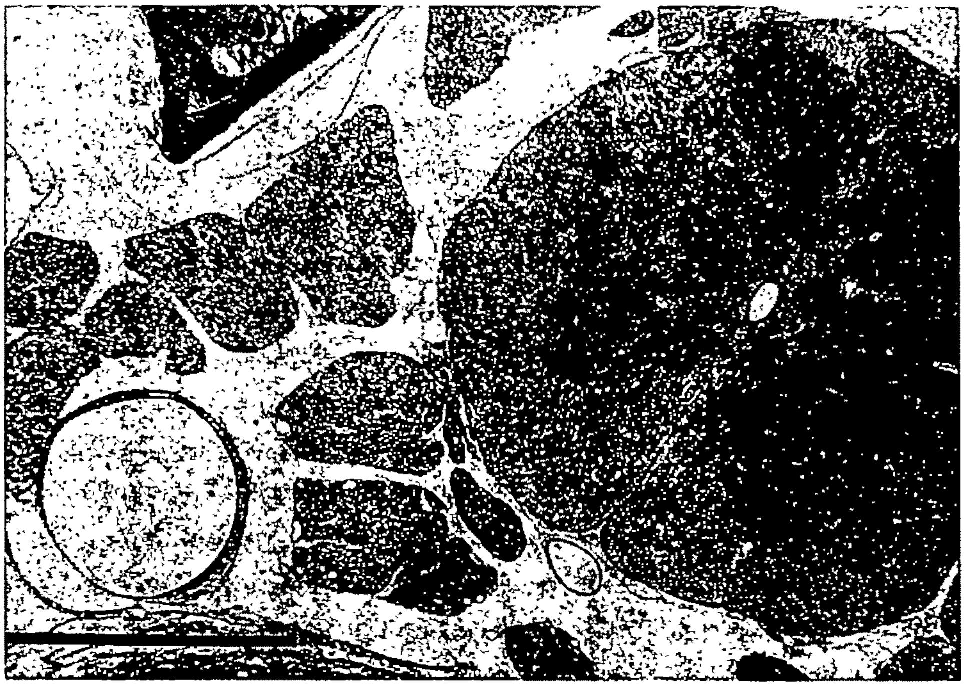

FIG. 2. Photomicrograph of a transverse section of rat spinal cord 1 month after subarachnoid catheterization and injection of midazolam, stained with haematoxylin and eosin. Scale bar = 1 mm. The original position occupied by the subarachnoid catheter is shown among the nerve roots, surrounded by arachnoid infiltrate.

which has been removed during sectioning; this is probably a reaction to the catheter, but the possibility remains that it may be the result of the administration of drug or vehicle.

The effect of vehicle. Figure 3 shows the current threshold for pain in the skin of the tail in one rat before and after the intrathecal injection of vehicle and midazolam 25 μl (125 μg) intrathecally. The current threshold for pain in the tail was not altered after the intrathecal injection of vehicle, but increased markedly after the intrathecal injection of midazolam. This single result was confirmed by statistical analysis of the grouped data (table I). The mean current threshold for pain has been calculated before and after the intrathecal injection of vehicle, and after the intrathecal injection of midazolam 125 μg for each of the five rats. These results were normalized by dividing the figures obtained before and after the intrathecal injections of vehicle and of midazolam by the control figures to allow grouping of the results for statistical analysis. The mean thresholds varied between animals because of differences in electrode and tail resistances and

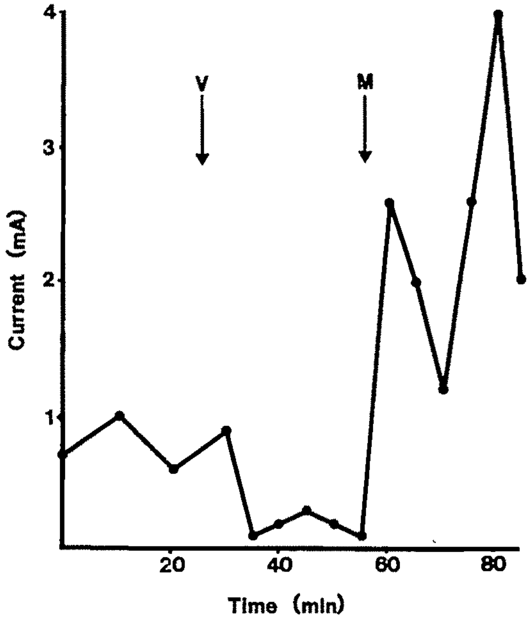

FIG. 3. Graph of the current threshold for pain in the skin of the tail of one rat, before and after the intrathecal injection of 25 μl of vehicle (V) and after the intrathecal injection of midazolam (M) 25 μl (125 μg).

TABLE I. *The mean current thresholds for pain in the tail of five rats before (C) and after the intrathecal injection of vehicle (V) and after the intrathecal injection of midazolam (M). Each figure in columns C, V and M was normalized by dividing it by the corresponding figure in column C for that rat, thus producing the figures in colums C′, V′, and M′. The application of Student's* t *test for paired data to* C′ v. V′ *and* V′ v. M′ *shows that there is a statistically significant* ($P < 0.025$) *increase in the current threshold for pain in the skin of the tail after intrathecal midazolam*, but no significant change after intrathecal injection of vehicle*

Rat	C	V	M	C′	V′	M′*
1	0.90	1.03	9.83	1.00	1.15	10.93
2	0.77	0.22	2.24	1.00	0.28	2.93
3	1.04	1.25	8.00	1.00	1.20	7.66
4	0.22	0.19	0.75	1.00	0.31	3.46
5	0.37	0.62	1.64	1.00	1.70	4.46

also differences between the animals themselves. These changes also occurred to a smaller extent within the same animal as the study progressed. It is therefore more appropriate to use comparisons of the figures in columns M′ with S′ and M′ with RO′ in table II, rather than M′ with C′. The application of Student's *t* test for paired data to the normalized results shows that there is a statistically significant ($P < 0.025$) increase in the current threshold for pain in the skin of the tail after intrathecal midazolam (V′ *v.* C′), but that there was no significant change in the current threshold for pain after intrathecal vehicle (M′ *v.* V′).

Differential analgesia. Figure 4 shows the current threshold for pain in the neck and the tail for one rat before and after the intraperitoneal injection of saline, and the intrathecal injection of midazolam 50 μg (10 μl).

Figure 5 shows the results from another rat which received the benzodiazepine antagonist RO 15–1788 5 mg i.p. 30 min before intrathecal midazolam. The features shown on figures 4 and 5 are supported by the grouped data (table II) when analysed statistically as above, *viz.*:

(a) intrathecal injection of midazolam caused an increase in the current threshold for pain in the skin of the tail but not in the neck ($P < 0.02$; paired *t* test, M′ *v.* S′ in tables II (i) and II (ii));

(b) the increase in current threshold for pain in the skin of the tail was prevented by the prior i.p. injection of RO 15–1788 (paired *t* test M′ *v.* RO′ in table II (iv)).

(c) there was no change in the current threshold for pain in the skin of the tail or neck after i.p. normal saline or RO 15–1788 (paired *t* test S′ *v.* C′ in tables II (i) and II (ii) and RO′ *v.* C′ in table I (iii) and II (iv)).

The speed of injection and volume of injectate were found by experience to be crucial in obtaining this differential blockade. Figure 6 shows the result of a study performed before the investigation of differential blockade; the rat received midazolam 25 μl intrathecally without control of the speed of injection. The current

TABLE II. *Mean current thresholds for pain in the skin of the neck (i) and tail (ii) in five rats which received i.p. saline and the skin of the neck (iii) and tail (iv) in five rats which received i.p. RO 15–1788. C = control measurements; S = measurements made after i.p. injection of saline; RO = measurements made after the i.p. injection of RO 15–1788; M = measurements made after the intrathecal injection of midazolam. C′, S′, M′ and RO′ represent data normalized as in table. I. By Student's* t *test for paired data:*
$P < 0.02$–*M′* v. *S′ in (ii)*; $P > 0.05$ *(ns)—S′* v. *C′; M′* v. *S′; Ro′* v *C′; M′* v. *Ro′*

(i) Neck

C	S	M	C′	S′	M′
0.65	0.70	0.76	1.00	1.08	1.17
0.34	0.27	0.48	1.00	0.78	1.41
0.13	0.13	0.20	1.00	0.94	1.50
0.24	0.30	0.40	1.00	1.24	1.65
0.67	0.70	0.68	1.00	1.04	1.02

(ii) Tail

C	S	M	C′	S′	M′
0.15	0.20	1.42	1.00	1.37	9.70
0.55	0.65	2.42	1.00	1.18	4.40
0.03	0.05	0.39	1.00	1.88	5.68
0.58	0.76	2.75	1.00	1.32	4.78
0.20	0.50	2.37	1.00	2.50	11.84

(iii) Neck

C	Ro	M	C′	Ro′	M′
0.57	0.57	0.70	1.00	1.00	1.24
0.60	0.75	0.77	1.00	1.25	1.28
0.63	0.60	0.40	1.00	0.95	0.63
0.125	0.08	0.08	1.00	0.60	0.60
0.583	0.60	0.57	1.00	1.03	0.97

(iv) Tail

C	Ro′	M	C′	Ro′	M′
0.04	0.05	0.06	1.00	1.18	1.50
0.29	0.39	0.43	1.00	1.34	1.48
0.14	0.30	0.33	1.00	2.19	2.43
0.47	0.60	1.12	1.00	1.29	2.40
0.35	0.36	0.48	1.00	1.02	1.38

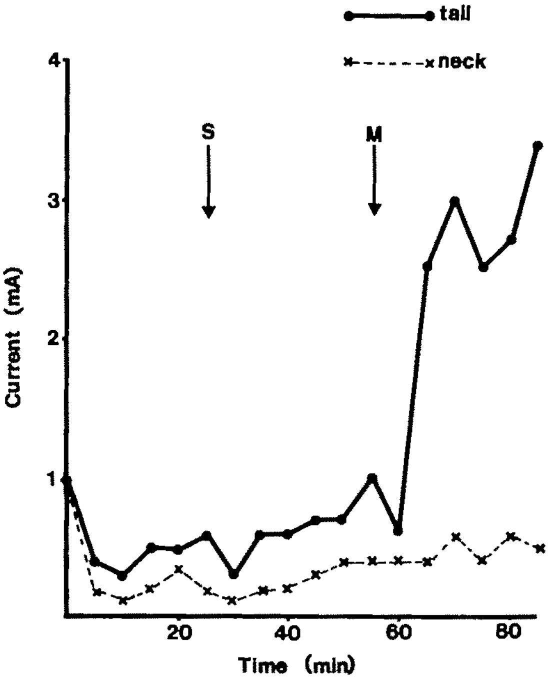

FIG. 4. Graph of the current threshold for pain in the skin of the tail and the neck of one rat before and after the i.p. injection of saline (S) and after the intrathecal injection of midazolam (M) 10 µl (50 µg).

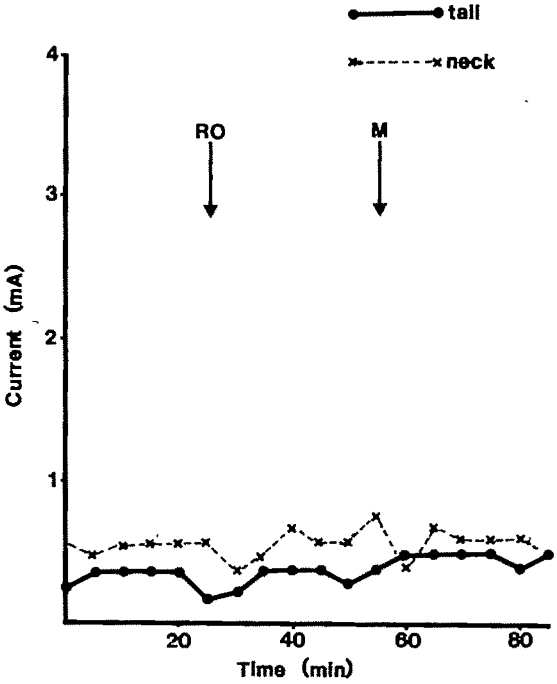

FIG. 5. Graph of the current threshold for pain in the skin of the tail and the neck in one rat before and after the i.p. injection of RO 15-1788 (RO) 5 mg and after the intrathecal injection of midazolam (M) 10 µl (50 µg).

threshold for pain in the neck and the tail both increased after this injection and the subsequent injection of 2% plain lignocaine solution 25 µl to verify the position of the catheter led to a total spinal block, with extreme pallor and paralysis of all four limbs.

Investigations in the frog

The results from three experiments on frog sciatic nerve are shown in figure 7. Compound action potentials evoked by supramaximal stimulation of the distal ends of each sciatic nerve are shown as single sweeps of the oscilloscope: A during the control period before any application of substances to the nerve; B after the application of vehicle to the nerve trunk between the stimulating and recording electrodes; C after the application of midazolam 5 mg ml^{-1}, and D after the application of 2% plain lignocaine solution to the nerve trunk. Neither midazolam nor the vehicle caused a diminution in the size of the compound action potential, unlike lignocaine which caused a typical local anaesthetic block.

DISCUSSION

The results from the first series of rats in which tail electrodes only were used, indicate that the intrathecal injection of midazolam causes an increase in the current threshold for pain in the tail, while the intrathecal injection of vehicle had no effect. This may be the result of spinally-mediated analgesia or general central nervous system depression from rostral spread of the drug. No obvious depression of the central nervous system occurred after the intrathecal injections of midazolam (the animals were not asleep and moved around the cage normally when released), but this possibility led us to design the second series of experiments with two sets of stimulating electrodes—one set on the tail and the other pair on the skin of the neck. It can be seen from the results of the second series of rats that intrathecal midazolam caused a differential effect when care was taken to control the speed and volume of injection; the increase in the current threshold for pain only occurred in the skin of the tail and not in the neck and this, therefore, implies a spinal mechanism for the analgesia.

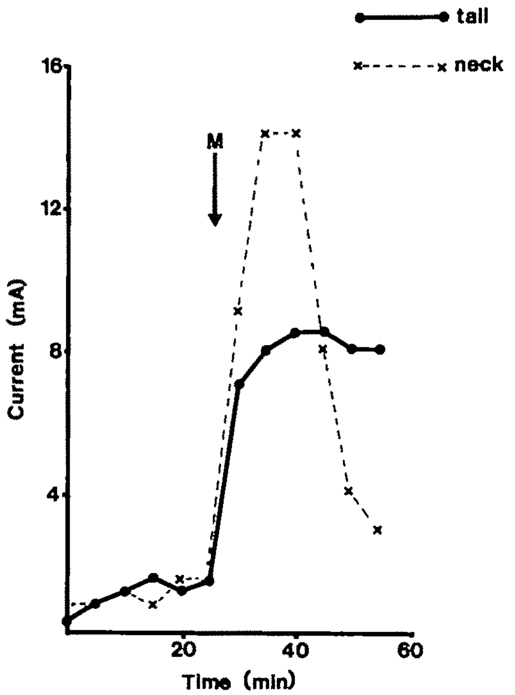

FIG. 6. Graph of the current threshold for pain in the skin of the tail and the neck in one rat before and after the intrathecal injection of midazolam (M) 25 μl (125 μg) without control of injection rate.

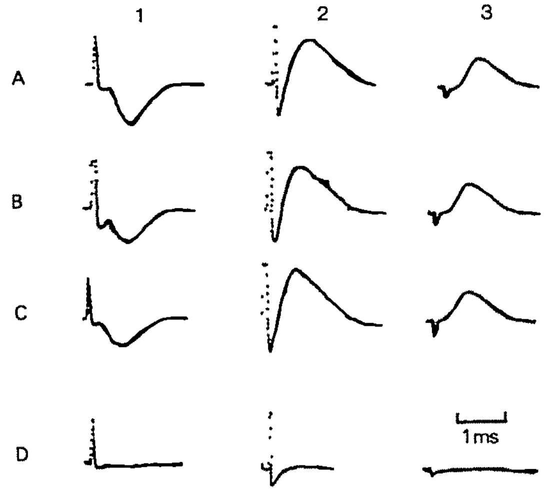

FIG. 7. Compound action potentials evoked by stimulation of three frog sciatic nerves: A = control; B after application of vehicle 0.5 ml (pH 3.5) to the nerve trunk; C = after application of midazolam 0.5 ml (5 mg ml^{-1}) to the nerve trunk; D = after application of 2% lignocaine solution to the nerve trunk. Distances between stimulating and recording electrodes = 4–5 cm.

It may be said that the performance of these experiments only 2–4 h after the surgical preparation and intrathecal injection of lignocaine would mean that the measurements had been made in the presence of an altered baseline. The animals were all moving around their cages and eating and drinking normally within 1 h of this preparation and the sudden change in the current threshold for pain in the tail and not in the neck following intrathecal midazolam must have been attributable to the midazolam and not just to the residual effects of the surgical preparation and intrathecal lignocaine. The volume of 2% lignocaine used (10 μl) to confirm the intrathecal position of the catheter (which was subsequently verified 1 month later by histopathological examination) is much smaller than Bahar, Rosen and Vickers (1984) found necessary to cause paralysis of the rear limbs (32 ± 3 μl). Since confirmation of the intrathecal position of all catheters was not reported in that study, one possible explanation for these differences may be that a proportion of their catheters were extradural and not intrathecal.

Two possibilities exist for the mechanism of spinally-mediated analgesia: a local anaesthetic effect on afferent nerves going into the spinal cord; and interference with neurotransmission of nociceptive afferent information, possibly mediated by combination with benzodiazepine receptors. Frog sciatic nerve was chosen as a convenient preparation for the study of possible local anaesthetic effects and the possibility of a local anaesthetic action was ruled out by the results of these studies. We were unable to demonstrate any local anaesthetic effect of midazolam which was applied at high concentration (5 mg ml^{-1}) to the sciatic nerve trunk, in contrast to the local anaesthetic blocking action of lignocaine. The second possibility is much more likely, since we were able to block the analgesic effect of intrathecal midazolam by prior administration of the benzodiazepine antagonist RO 15–1788 (figs 4, 5; table II).

Therefore we conclude that intrathecal midazolam causes spinally-mediated analgesia by binding to benzodiazepine receptors in the spinal cord. It may be that this combination with benzodiazepine receptors potentiates the antinociceptive effects of gamma amino butyric acid (Buckett, 1980); more work needs to be performed to elucidate the precise mechanism involved.

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EFFECT OF VERAPAMIL ON Ca^{2+} INFLUX TO RAT PHRENIC NERVE–DIAPHRAGM PREPARATION

F. A. WALI AND A. H. SUER

SUMMARY

The effect of verapamil on contractility and on influx of calcium (Ca^{2+}) to the rat phrenic nerve–hemidiaphragm preparation was studied in vitro, *at rest and during electrical stimulation at 0.2–100 Hz. Calcium content of the bathing solution was measured using the Technicon method (SMAC, Sequential Multiple Analyser/Computer). The results showed that verapamil (a) reduced the twitch and tetanic contractions in a non-competitive manner, and (b) reduced the influx of Ca^{2+} to the rat hemidiaphragm preparation. Greater reductions occurred as the rate of stimulation increased.*

The pharmacology of verapamil, and its therapeutic use, have been studied extensively in man and experimental animals (Bondi, 1978; Singh, Ellrodt and Peter, 1978; Bikhazi, Leung and Foldes, 1982, 1983; Kraynack, Lawson amd Gintautas, 1982, 1983; Carpenter and Mulroy, 1983; Durant, Nguyen and Katz, 1984; Wali, 1985, 1986). Verapamil inhibits Ca^{2+} influx by blocking its entry through the voltage-dependent slow Ca^{2+} channels which have been recently demonstrated in skeletal muscle (Sato and Ono, 1982). Although the main site of action of verapamil at the neuromuscular junction is debatable (Foldes, 1984; Durant, Nguyen and Katz, 1984; Baraka, 1985), the consensus of opinion is that the drug has both prejunctional and postjunctional actions (Baraka, 1985; Wali, 1985, 1986). Quantitative data on the influx of Ca^{2+} to a rat phrenic nerve–diaphragm preparation is lacking, and we thought it useful to estimate the amount of Ca^{2+} entering this preparation at rest and during electrical nerve stimulation in the presence and absence of verapamil.

MATERIALS AND METHODS

Preparation

The left phrenic nerve–diaphragm preparation of male Sprague–Dawley rats (100–200 g) was dissected and placed in cold Krebs–Henseleit solution. The preparation was set up in an organ bath containing 80 ml of Krebs–Henseleit solution maintained at 38 ± 2 °C and bubbled with 5% carbon dioxide in oxygen. The pH of the Krebs solution was 7.2.

Stimulation and recording

The phrenic nerve, and the diaphragm, were stimulated at 0.2–100 Hz with 5–10 V (supramaximal) and 0.2-ms square pulse duration. Mechanical responses produced by electrical nerve stimulation (or muscle stimulation) were recorded isometrically by means of a force–displacement transducer (D1 50 g) and a Washington pen recorder (Palmer Bioscience, U.K., model 400 MD 2C). The frequency response of the recorder amplifier was linear up to 28 ± 2 Hz, decreasing to a minimum with −3dB at about 38 Hz. Stimuli were delivered to the nerve or to the muscle via a pair of stimulating electrodes connected to the terminals of a small stimulator (Sartorius).

Measurement of contractile responses

After the preparation had been set up it was left to settle and to equilibrate for 15 min before the addition of any drug. Control, and directly- and indirectly-elicited twitch contractions were evoked and recorded in the absence of any drug. These reponses were stable for a long period of time; for example 3–4 h—a time usually exceeding the duration of each investigation. The effect of verapamil 0.1–200 μmol $litre^{-1}$ on the amplitude

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F. A. WALI, B.SC., M.SC., PH.D.; A. H. SUER, M.B., D.A.; Anaesthetics Unit, The London Hospital Medical College, Whitechapel, London E1 1BB. Accepted for Publication: March 11, 1987.

of the indirectly-elicited twitch and tetanic (0.2–100 Hz) contractions was studied. Concentration–effect curves were established and the mean IC_{50} values (concentration to produce 50% maximum inhibition) were determined. The mean frequency of stimulation which produced 50% maximum contraction ($Freq._{50}$) was also determined. A cumulative method was not used in establishing the concentration–effect curves for verapamil, since the drug may accumulate in tissue with time (Williams et al., 1983). Instead, single concentrations (in small volumes of 0.2 or 0.4 ml) of drug were injected in a random manner. Sufficient time was allowed for the effects to reach a maximum effect (usually in 2–4 min) depending on the concentration used. Following the maximum effect, the drug was washed off (two or three times) with Krebs–Henseleit solution until recovery of twitch and tetanic responses was obtained. The concentration of drugs was obtained at the muscle, that is, the bath concentration.

Measurements of Ca^{2+} influx

It should be noted that, in these experiments, the Ca^{2+} content of the fluid bathing the preparation was measured, and not the uptake of verapamil, as reported by other workers using electrophysiological techniques, the lanthanum method or measurements of radioactive calcium-45 (Batra, 1973; Burton and Godfraind, 1974; Endo, 1977; Martonosi, 1984). Any change in the Ca^{2+} content of the buffer caused by verapamil or electrical nerve stimulation, was measured using the Technicon method (Sequential Multiple Analyser/Computer). This technique is based on the work of Gitelman (1967) and modified by Kessler and Wolfman (1964), who incorporated 8-hydroxyquinoline, to eliminate interference from magnesium. The method used to measure the Ca^{2+} concentration utilized the metal complexing dye "Cresolphthalein Complexone", which has the ability to bind calcium ions in an alkaline medium. The product of this interaction is a pink coloured Ca^{2+}–dye complex which has a maximum absorption at a specific wavelength (570 nm). The technique is used to measure total and ionized Ca^{2+} and other ions in blood or serum of patients.

Briefly, the serum is added to a diluted solution of hydrochloric acid containing 8-hydroxyquinoline. The hydrochloric acid releases the protein-bound Ca^{2+} and the quinoline binds the free Mg^{2+} present in the serum. The free Ca^{2+} is dialysed across a semipermeable membrane (type H) into the analytical stream of "Cresolphthalein Complexone" containing additional 8-hydroxyquinoline. Upon the addition of diethylamine to the analytical stream, a coloured complex is formed between the Ca^{2+} and the dye. The reaction stream is heated at 37 °C, to develop fully the coloured complex. The substance of the reaction product is measured at 570 nm in a flow cell that has a 10-mm light path and an inside diameter of 0.5 mm.

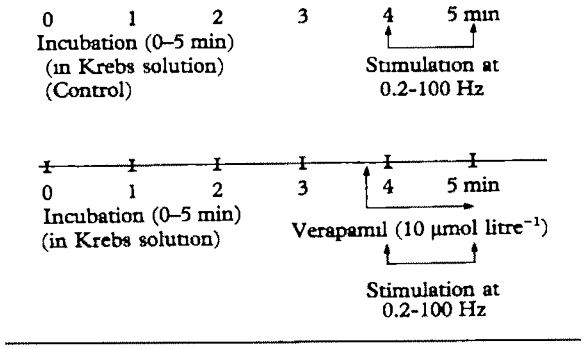
The reagents used in this procedure must be free from particulate and other foreign matter, or obvious colour changes. Each reagent was examined thoroughly before use, and any reagent displaying any signs of contamination, instability or colour changes was replaced.

The sensitivity of this method is quite high—in the order of 0.017 absorbance unit per unit of concentration. The test range of this method is 0–15 mg dl^{-1} and the average drift within a recalibration cycle is 0.2 mg dl^{-1}.

Design of experiment for measuring Ca^{2+} content or influx

Unstimulated preparation (at rest). The preparation was incubated for 5 min in control Krebs–Henseleit solution containing Ca^{2+} 2.54 mmol $litre^{-1}$. The Ca^{2+} content of buffer was measured (without preparation) and after 5 min incubation of the preparation. The difference between the measurements before and after incubation was calculated, and this was attributed to the influx of Ca^{2+} to the preparation from the bathing medium. Ca^{2+} can be transferred passively along its concentration gradient (outside 2.54 mmol $litre^{-1}$, inside 0.7 μmol $litre^{-1}$). In this respect influx (or uptake) would be non-specific, the Ca^{2+} being taken up by both nerve and muscle fibres. It was for this reason, that no attempt was made to measure the actual uptake of Ca^{2+}, as described in the literature (Batra, 1973). The procedure was repeated, in the presence of verapamil 10 μmol $litre^{-1}$ for 5 min, and the difference between the control Ca^{2+} content of buffer and that in the presence of verapamil was calculated. The Ca^{2+} content of buffer will be reduced in the presence of the preparation, but it will be less reduced in the presence of verapamil, since the latter will prevent influx of Ca^{2+} to the preparation. Suppose that the Ca^{2+} content of buffer was A, that in preparation was B and that in verapamil with

TABLE I. *Time intervals of incubation and stimulation of preparation, in the absence and presence of verapamil, respectively*



preparation was *C*. It can be expected that the Ca^{2+} content of *C* is greater than that of *B*, but smaller than that of *A*. This was found to be the case, and the difference in the Ca^{2+} contents must be attributable to the influx mechanism, that is, uptake by the preparation. The glassware and other materials cannot be considered as possible factors of disappearance of ions, since there was a differential change in uptake of ions which cannot be obtained in the presence (or absence) of glassware. Thus the system used was dynamic—increases or decreases were obtained in response to drugs or nerve stimulation.

Stimulated preparations. The Ca^{2+} content was measured before and immediately after repetitive nerve stimulation at 0.2–100 Hz, in the absence (control) and presence of verapamil (e.g. 10 µmol litre^{-1}). Table I shows the plan of the experiment.

The influx of Ca^{2+} was initially measured in mmol litre^{-1}, and this was later converted to µg/mg tissue min^{-1}, or more conveniently as pmol mg^{-1} min^{-1} or as pmol mg^{-1} impulse^{-1}.

Drugs and solutions

All drugs and solutions were made up in deionized distilled water. The Krebs solution used had the same composition (mmol litre^{-1}) as that previously used (Elliott and Wali, 1983), which contained calcium chloride (Ca^{2+}) 2.54 mmol litre^{-1}. Verapamil hydrochloride (ampoules, Cordilox, Abbot) was used, one ampoule containing 2.5 mg in 2 ml of solution. We used ampoules, instead of pure powder of verapamil, since it was desired to mimic the clinical situation in the rat diaphragm preparation. However, the results may be influenced by the vehicle contained in the ampoule.

Statistical analysis

Means ± SEM of results were calculated. A Student's *t* test was used for the significance of paired (or unpaired) sets of observations. A probability $P < 0.05$ was considered significant in the present investigation.

RESULTS

Effect of verapamil on mechanical twitch and tetanic contractions

Figure 1 shows examples of the mechanical responses of indirectly-elicited twitch (0.2 Hz) and tetanic (2–100 Hz) contractions, of various durations (20–60 s), in the absence and presence of verapamil 10 µmol litre^{-1}. At this concentration, verapamil had no significant effect on the twitch tension (fig. 1A). However, verapamil markedly reduced the contractions produced at 10 Hz or more (fig. 1E-L). In figure 1E verapamil reduced the tetanic tension and produced a marked fade (in F). The control tetanus was 3.9 g tension (fig. 1G) and this was reduced by 59 % in the presence of verapamil (fig. 1H). Tetanic stimulation at 50 Hz (fig. 1I, J) produced 3.1 g tension (fig. 1I) and this was reduced by 68 % in the presence of verapamil (fig. 1J). Stimulation at 100 Hz (fig. 1K, L) produced 2.6 g tension (fig. 1K) and this was reduced by 73 % in the presence of verapamil (fig. 1L). It should be noted that the control twitch tension varied from preparation to preparation, and on average the range was 1.0–1.4 g tension. In addition, there were some variations in the single twitch contractions, and this did not result from using submaximal stimulation, but as a result of biological variations between different preparations.

Figure 2 shows concentration–effect relations (on a log scale) of the effect of verapamil 0.1–1000 µmol litre^{-1} on indirectly and directly-elicited twitch tension. Verapamil produced concentration-dependent block of the twitch tension. However, the effect of verapamil on the directly-elicited twitch tension was minimal, that is about 15 % of maximum indirect twitch inhibition. The mean (± SEM) IC_{50} value (concentration to produce 50 % maximum inhibition) of verapamil-induced inhibition of indirect twitch tension was 65 ± 5 µmol litre^{-1} ($n = 6$).

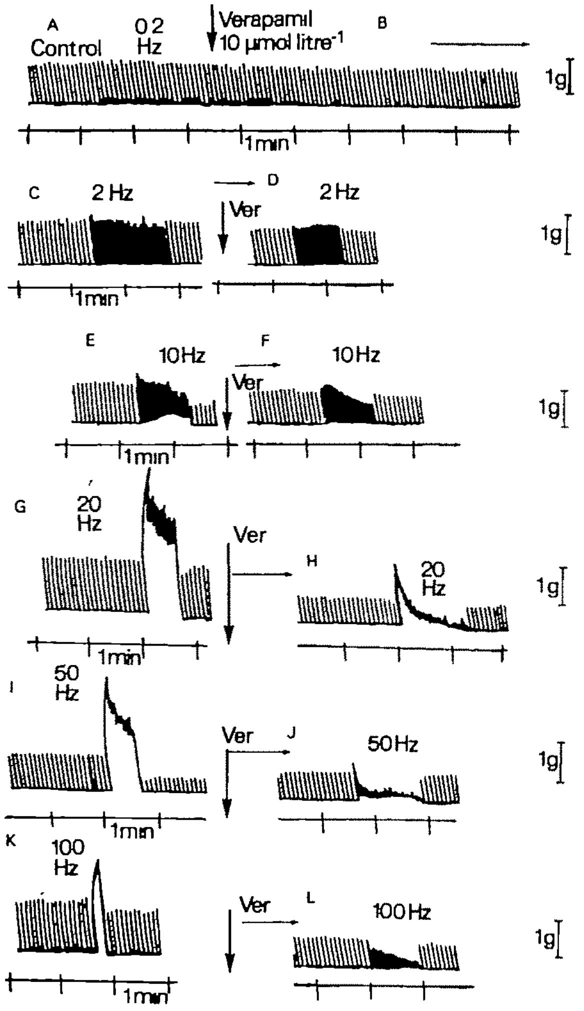


FIG. 1. Examples of mechanical recordings of indirectly-elicited twitch and tetanic contractions, in the rat diaphragm preparation, in the absence and presence of verapamil 10 μmol litre^{-1}. A: Control twitch tension (1.1 g, elicited at 0.2 Hz with 5-V (supramaximal) and 0.2-ms square pulse duration. B: Verapamil had little effect on the twitch tension. C: Stimulation at 2 Hz produced 1.3 g tension. D: Verapamil did not significantly reduce the tension produced in C. E: Stimulation at 10 Hz produced 1.4 g tension. F: Verapamil reduced the tension by 40 % (of E). G: Stimulation at 20 Hz produced 3.9 g tension. H: Verapamil reduced the tension by 59 % (of G). I: Stimulation at 50 Hz produced 3.1 g tension. J: Verapamil reduced the tension by 68 % (of I). K: Stimulation at 100 Hz produced 2.6 g tension. L: Verapamil reduced the tension by 73 % (of K).

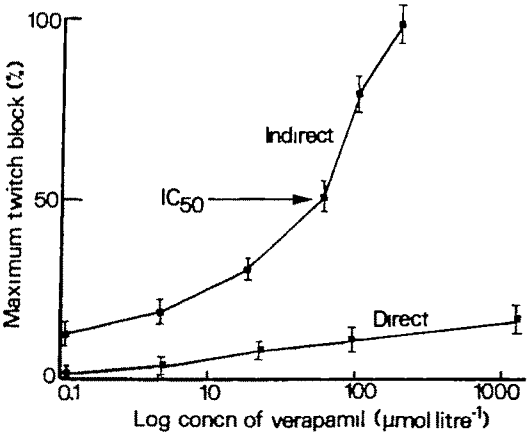


FIG. 2. Concentration–effect relationships (on a log scale) of verapamil-induced depression of twitch tension. Verapamil 0.1–1000 μmol litre^{-1} produced concentration-dependent block of indirectly- and directly-elicited twitch tension. Greater reduction (up to 100 %) occurred in the indirectly-elicited twitch tension; the directly-elicited twitch tension was only slightly reduced by verapamil. Each point is a mean ± SEM of six experiments.

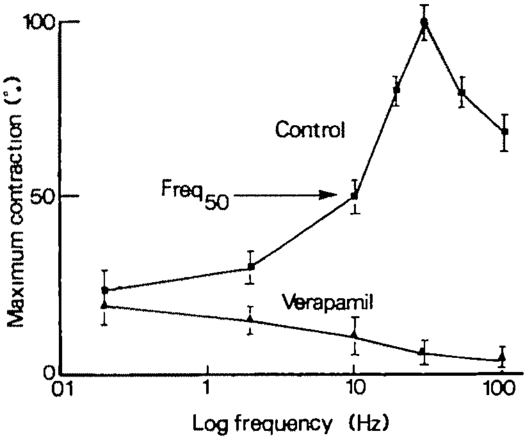


FIG. 3. Frequency–response relationships (on a log scale) of the contractions produced by nerve stimulation at 0.1–100 Hz in the absence and presence of verapamil 10 μmol litre^{-1}. Increasing the frequency of nerve stimulation (up to 30 Hz) increased the size of the contractions. However, at higher rates of stimulation, the contractions were decreased gradually. Verapamil steadily reduced the control contractions in such a manner that more marked reductions occurred with higher rates of stimulation. Each point is a mean ± SEM of six experiments.

Figure 3 shows frequency–response relations (on a log scale) for the contractions produced by nerve stimulation at 0.1–100 Hz. It can be seen that increasing the frequency of nerve stimulation resulted in greater tetanic contraction, for up to 30 Hz; thereafter, the contraction was decreased with increasing tetanic stimulation. Verapamil 10 μmol litre^{-1} steadily and progressively decreased the contractions produced by nerve stimulation, such that the greatest reductions

TABLE II. *Effect of verapamil on Ca^{2+} influx into phrenic nerve-diaphragm preparation of the rat (mean ± SEM,* n = 6*). Influx of Ca^{2+} increased steadily with increasing frequency of stimulation in the control preparations (C). In the presence of verapamil (V)* 10 μ*mol litre*$^{-1}$*, Ca^{2+} influx was decreased steadily with increasing frequency of nerve stimulation.* *P < *0.05;* **P < *0.001, with respect to the control values*

	Ca^{2+} influx (μmol mg^{-1} min^{-1})		[(C-V)/C] × 100
	Control (C)	Verapamil (V)	Block (%)
Unstimulated	3.40 ± 0.1	3.3 ± 0.2	2.9 ± 0.3
Stimulated at			
0.2 Hz	3.7 ± 0.2	3.0 ± 0.1	18.9 ± 0.9*
20 Hz	4.2 ± 0.1	2.7 ± 0.4	35.2 ± 2.1**
50 Hz	4.5 ± 0.2	2.6 ± 0.3	41.9 ± 2.2
100 Hz	5.1 ± 0.3	2.4 ± 0.1	52.3 ± 3.4

occurred at highest rates of stimulation, decreasing towards zero contraction at near 100-Hz stimulation. The mean frequency of stimulation which produced 50% maximum contraction ($Freq._{50}$) in the control Krebs solution was 12 ± 2 Hz. The mean $Freq._{50}$ value in the presence of verapamil was not obtained, as a result of a continuous decline in the tetanus.

Effect of verapamil on Ca^{2+} influx

The data obtained with the influx of Ca^{2+} to a phrenic nerve–diaphragm preparation are shown in table II. As indicated, influx of Ca^{2+} was calculated from the original Ca^{2+} content in buffer solution (2.54 mmol litre^{-1}) and from the Ca^{2+} taken up into the preparation, as measured in μmol mg^{-1} min^{-1}. To aid understanding of the table, the results are divided into unstimulated and stimulated preparations. Before setting out to analyse the results, it would be appropriate to give an example of how some calculations were made:

Calcium content of the buffer: Molecular weight of Ca^{2+} content is 219 ($CaCl_2.6H_2O$ = 219 g litre^{-1} = 1 mole and thus 1 mmol = 219 mg litre^{-1}. For 80 ml of solution we have 17.52 mg. Since the concentration of Ca^{2+} in the bath was 2.54 mmol litre^{-1}, 17.52 × 2.54 = 44.5 mg is the total amount of Ca^{2+} in the bath.

Now let us suppose that the Ca^{2+} content left in buffer after incubation of the preparation, for 5 min, was 1.57 mmol litre^{-1}. We subtract this from the control value of 2.54 mmol litre^{-1}: 2.54 − 1.57 = 0.97 mmol litre^{-1}. The latter in terms of weight is equal to 16.99 mg net influx (in unstimulated preparations). This result must be divided by the weight of preparation and the time of incubation. Thus uptake = 16.99 mg/(1000 mg × 5 min) = 0.003398 mg/mg tissue min^{-1}, = 3.398 μg mg^{-1} min^{-1}. Now let us consider what happens in the presence of verapamil: the influx of Ca^{2+} is reduced and, supposing the measured Ca^{2+} was 1.61 mmol litre^{-1}, then 2.54 − 1.61 = 0.93 mmol litre^{-1}, in terms of weight, is 16.2936 mg net influx (in unstimulated preparations). The new uptake is: 16.2936 mg/(5000 mg min^{-1}) = 3.2587 μg mg^{-1} min^{-1}. Thus in the presence of verapamil, the uptake was reduced by 4.1% of control value. In table I, the effect of verapamil on the influx of Ca^{2+} was not significant in the unstimulated preparations. However, verapamil significantly reduced the uptake of Ca^{2+} into preparations stimulated at 0.2, 20, 50 and 100 Hz. For example, at 0.2 Hz, the control Ca^{2+} influx was 3.7142 μg mg^{-1} min^{-1}, and the influx in verapamil was 2.9784 μg mg^{-1} min^{-1}, thus giving a percentage change of 19.8% ($P < 0.05$).

In order to calculate the Ca^{2+} influx per nerve impulse, similar calculations were made—that is, proceed as before, but also divide the uptake by the number of pulses per minute. For example, at 20 Hz, we calculated an uptake of 0.7358 μg mg^{-1} min^{-1} and this becomes 0.7358/1200 = 0.0006131 μg mg^{-1} pulse^{-1}, that is 0.6131 pg mg^{-1} pulse^{-1}.

In the presence of verapamil, this value was greatly reduced:

$$\text{uptake} = \tfrac{0.5256}{1200} = 0.000438\ \mu\text{g mg}^{-1}\,\text{pulse}^{-1}$$
$$= 0.438\ \text{pg mg}^{-1}\ \text{pulse}^{-1},$$

and this is 28.6% of the control uptake ($P < 0.001$). Pooled results are shown in table III. The amount of Ca^{2+} entering the preparation was high at low rates of stimulation, and this decreased markedly at high rates of stimulation. Verapamil

TABLE III. *Effect of verapamil on Ca^{2+} influx per nerve impulse (mean ± SEM, n = 6). Ca^{2+} influx per nerve impulse was high at low rates of stimulation and declined rapidly at high rates of nerve stimulation. Verapamil 10 µmol $litre^{-1}$ steadily and rapidly decreased the Ca^{2+} influx per nerve impulse, the effect being inversely related to frequency of nerve stimulation.* $^{*}P < 0.05$; $^{**}P < 0.001$, *with respect to control values*

	Ca^{2+} influx (pmol mg^{-1} $impulse^{-1}$)		$[(C-V)/C] \times 100$
	Control (C)	Verapamil (V)	Block (%)
Stimulated at			
0.2 Hz	26.3 ± 2.1	22.9 ± 1.9	$12.5 \pm 1.1^{*}$
20 Hz	0.65 ± 0.01	0.44 ± 0.02	$32.1 \pm 2.3^{**}$
50 Hz	0.39 ± 0.03	0.23 ± 0.01	$41.1 \pm 3.4^{**}$
100 Hz	0.28 ± 0.01	0.13 ± 0.02	$53.2 \pm 3.7^{**}$

10 µmol $litre^{-1}$ gradually reduced the Ca^{2+} influx and this depended on the frequency of nerve stimulation.

DISCUSSION

The cytoplasmic concentration of free Ca^{2+} in the living cell at rest is 10^{-7} mol $litre^{-1}$ or less (Martonosi, 1984), and this is 10^{5} times lower than the free Ca^{2+} of the environment. The large Ca^{2+} gradient across cellular boundaries is established and maintained by Ca^{2+} pumps located on the surface of the cell membrane, in sarcoplasmic reticulum and in mitochondria.

The two known pathways for Ca^{2+} entry to the cytoplasm (McCleskey, 1985) are from the sarcolemmal Ca^{2+} channels, which are located in the transverse tubules (Stanfield, 1977), and from the sarcoplasmic reticulum. Verapamil, an organic calcium channel blocker, is known to inhibit calcium influx through voltage-dependent slow calcium channels, for example those in skeletal muscle (Sato and Ono, 1982). At rest, most of the Ca^{2+} channels are closed, but during activity (by electrical stimulation) these channels are opened to allow movement of Ca^{2+}. The effect of verapamil is dependent on the concentration used, the time allowed for exposure and on the type of nerve or muscle fibre used. The effect of verapamil is also dependent on the condition of the nerve or the muscle fibre; that is, whether at rest or during activity.

In the present investigation, we decided to study the effect of verapamil on the contractile responses of the indirectly- and directly-elicited twitch and tetanic contractions, and the effect of verapamil on influx of Ca^{2+} into rat phrenic nerve–hemidiaphragm preparation, at rest and during electrical stimulation. It should be noted that the above two aims are separate entities, and that the results from one should not be taken to interpret the other. For example, the results from the influx experiments should not be taken to explain how verapamil reduces the twitch or tetanic tension.

The methodology used in the present study was to measure the Ca^{2+} influx, and not the uptake. We used the Technicon method (SMAC), which is an accurate computer-controlled automatic analyser, to measure the Ca^{2+}content of the buffer, before and after the addition of verapamil, in the presence and absence of the preparation. The results showed that there was a different loss in the Ca^{2+} content in the absence than in the presence of verapamil 10 µmol $litre^{-1}$; that is, greater loss of Ca^{2+} occurred in the absence than in the presence of verapamil. This type of differential influx cannot be assigned to the absorbance by the glassware since, in the presence of verapamil the influx of Ca^{2+} decreased irrespective of the adherence of ions to glassware. Moreover, the presence of glassware did not produce a differential effect on influx of Ca^{2+}; that is, it did not increase or decrease the Ca^{2+} content of the buffer solution. Furthermore, there was a greater loss of Ca^{2+} in the buffer containing the preparation stimulated at 0.2 Hz, 20 Hz, 50 Hz and 100 Hz, than in the buffer containing the unstimulated preparation. Thus, during activity, the Ca^{2+} channels are opened, and Ca^{2+} will enter the preparation through the voltage-dependent calcium channels. In the unstimulated preparation, most of the Ca^{2+} channels are closed and the influx of Ca^{2+} can only occur by passive diffusion—along the electrochemical gradient of Ca^{2+} from a high Ca^{2+} in the extracellular medium (2.54 mmol $litre^{-1}$ to a low intracellular Ca^{2+} (0.1 µmol $litre^{-1}$). However, under normal physiological conditions, there is a 10^{5}-fold difference in the Ca^{2+} and this is well maintained by the action of membrane pumps.

The Ca^{2+} influx in the present study, is non-specific; that is, it is the result of influx of Ca^{2+} into both nerve and muscle fibres, and we do not know how much of Ca^{2+} was taken up by the nerve terminals alone. However, we were only concerned with the uptake of Ca^{2+} as a whole, into the whole preparation, in the presence of verapamil. In the unstimulated preparations, verapamil had little effect on the influx of Ca^{2+} (table II), indicating that this influx was attributable to a leakage of Ca^{2+} rather than through controlled Ca^{2+}, voltage-dependent channels. During activity, verapamil produced a significant decrease in the Ca^{2+} influx, indicating that it had actually blocked the Ca^{2+} channels, which had previously been opened up by electrical stimulations. The variations in the amplitude of the twitch contractions, observed in the present investigation, were obviously a reflection of biological variations of different preparations; that is, of different tissue sensitivities in the same species. These variations were not the result of the use of submaximal stimulation, since the stimulation used in the present study (5–10 V) was sufficient to excite all the nerve or muscle fibres (supramaximal stimulation was used). In addition, the variations observed in the present study were irregular and not repeated in every preparation. We wished to use the ampoule rather than a pure preparation of verapamil, since the ampoule is clinically available and ready for use in patients. However, our results may be influenced by the vehicle contained in the ampoule.

The effect of verapamil was concentration, time and frequency-dependent. Thus high concentrations of verapamil produced greater inhibition of the twitch and tetanic tensions (figs 2, 3). For example, incubation of the preparation for 5 min and repetitive nerve stimulation at 20 Hz resulted in an uptake of Ca^{2+} of 4.2 ± 0.1 µmol mg^{-1} min^{-1}, and this was reduced by 35% in the presence of verapamil 10 µmol litre^{-1}; greater reductions occurred at high rates than at low rates of stimulation (table II). The Ca^{2+} influx per nerve impulse (table III), decreased with an increase in the frequency of stimulation. Verapamil progressively reduced the influx per impulse and, with 100 Hz, a 53% block was obtained. This also meant that the effect of verapamil was use-dependent, that is not an all-or-nothing phenomenon (unlike that of the action potential). Thus a gradual and a progressive decrease of Ca^{2+} uptake can be obtained with different concentrations of verapamil and with different rates of nerve stimulation. Unlike tubocurarine, which competitively blocks acetylcholine nicotinic receptors at the neuromuscular junction, the effect of verapamil was not competitive. Once the channel is blocked by verapamil, increasing the frequency of nerve stimulation would not open the channels, but perhaps causes a further block of these channels. However, there is a limit beyond which an increase in the frequency of stimulation (e.g. > 30 Hz), would not result in an increase in the amount of acetylcholine released (Straughan, 1960). Acetylcholine release is dependent on the Ca^{2+} influx to nerve terminals, and at high rates of stimulation, the release is decreased (fig. 1G, I, K) per nerve impulse. An increase in the Ca^{2+} entry to the nerve terminals, for example as a result of membrane depolarization (Baker, Hodgkin and Ridgway, 1971), results in an increase in the acetylcholine release. Furthermore, there is a feedback control of transmitter release at the neuromuscular junction (Bowman, Marshall and Gibb, 1984). In the unstimulated preparations, it is not clear how verapamil reduced (although not significantly) the influx of Ca^{2+} into the nerve–muscle preparation. It is possible that verapamil may block some of the Ca^{2+} channels, or channel components, involved in transmitter release (Katz and Miledi, 1969). Furthermore, it is known that verapamil may have a local anaesthetic-like action (Singh and Vaughan-Williams, 1972; Bondi, 1978), thereby blocking the Na^+ channels, and thus stabilizing the resting membrane potential.

Baker, Hodgkin and Ridgway (1971) have measured the Ca^{2+} entry to the squid giant axon, using the technique of aequorin luminescence. The photoprotein aequorin is sensitive to µmol litre^{-1} concentrations of Ca^{2+}, and it emits light in the presence of minute amounts of Ca^{2+}. In sea water, which contains Ca^{2+} 11 mmol litre^{-1}, the Ca^{2+} per nerve impulse, at 20 °C, was calculated to be 0.006 pmol cm^{-2}, that is, 36 Ca^{2+} per square micron, or 1/700 of net Na^+ entry. Stimulation at 150 Hz increased the influx of Ca^{2+} by about 20-fold. In the present investigation, similar results were obtained. Although verapamil reduced the Ca^{2+} influx, for example at 100 Hz stimulation, it did not completely block the Ca^{2+} entry, indicating that leakage (passive entry) of Ca^{2+}, perhaps through other channels such as the Na^+ channel (Baker, Hodgkin and Ridgway 1971), may be possible. It is also possible that Ca^{2+} may enter through other, unidentified, channel components, such as those for acetylcholine release (Katz and Miledi, 1969). Further investigation is needed to elaborate on the above possibilities and to see if there were more than one type of calcium channel in the membrane. It will be interesting to know if verapamil can selectively block one type of Ca^{2+} channel and not the other.

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RELATIONSHIPS AMONG VENTILATION–PERFUSION DISTRIBUTION, MULTIPLE INERT GAS METHODOLOGY AND METABOLIC BLOOD-GAS TENSIONS

A. ST J. LEE, R. W. PATTERSON AND R. D. KAUFMAN

SUMMARY

The retention equations upon which the Multiple Inert Gas Method is based are derived from basic principles using elementary algebra. It is shown that widely disparate distributions produce indistinguishable sets of retentions. The limits of resolution of perfused compartments in the $\dot{V}A/\dot{Q}$ *distribution obtainable by the use of the multiple inert gas method are explored mathematically, and determined to be at most shunt and two alveolar compartments ("tripartite" distribution). Every continuous distribution studied produced retentions indistinguishable from those of its unique "matching" tripartite distribution. When a distribution is minimally specified, it is unique. Any additional specification (increased resolution—more compartments) of the distribution results in the existence of an infinitude of possible distributions characterized by indistinguishable sets of retention values. No further increase in resolution results from the use of more tracers. When sets of retention values were extracted from published multiple inert gas method continuous distributions, and compared with the published "measured" retention sets, substantial differences were found. This illustrates the potential errors incurred in the practical,* in vivo *application of the multiple inert gas method. In preliminary studies, the tripartite distribution could be determined with at least comparable accuracy by blood-gas (oxygen, carbon dioxide) measurements.*

Until 1974, physiologists described the ventilation–perfusion ($\dot{V}A/\dot{Q}$) aspects of the lung by grouping together the various blood/air interactive sites into two perfused "compartments", shunt and an "alveolar" compartment, and the unperfused deadspace (Briscoe, 1959; Farhi and Yokoyama, 1967). The landmark paper (Wagner, Salzman and West, 1974) on the multiple inert gas method of determining the detailed distribution of the cardiac output between shunt and 48 alveolar "compartments" offered far more information. Two quotations from that paper summarize their achievements; a third sets a warning:

> "Measurements with several foreign gases such as krypton and xenon (29) and methane, ethane and nitrous oxide (34) have been used to gain information about distributions of $\dot{V}A/\dot{Q}$ ratios. However, these analyses, as with the oxygen methods, have been limited to a small number of compartments." (p. 588.)

> "This paper describes a method for determining virtually continuous distributions of $\dot{V}A/\dot{Q}$ ratios." (p. 588.)

> "The question arises as to how it is possible to recover 50 compartments with far fewer independent equations. The answer to this is not clear and we do not propose to consider it in any detail in this paper." (p. 591.)

Since that time some 100 papers and chapters, on the multiple inert gas method, theoretical and applied, have appeared in the literature. Important characteristics of the method are described in the following quotations:

> "They interpreted the data in terms of a two-compartment model based on simple mixing equations, which took account of the mass

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Arnold St Jacques Lee, B.A., P.E.; Department of Anesthesiology, University of California, Los Angeles, California 90024, U.S.A., and Surgery Department, Morehouse School of Medicine, Atlanta, Georgia, U.S.A.; Richard W. Patterson, M.D.; Robert D. Kaufman, M.D.; Department of Anesthesiology, University of California, Los Angeles, U.S.A.

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conservation that must be present (Farhi and Yokoyama, 1967). They found that the lungs behaved as if there was one compartment with a nearly normal ventilation–perfusion ratio and another with a low ratio of less than 0.1, which received 10–29% of the total bloodflow.

However, the potential of inert gases for elucidating the pattern of ventilation–perfusion inequality goes far beyond deriving a two-compartment model." (Wagner and West, 1980) (p. 230.)

"In principle, the greater the number of gases, the more detailed and precise is the resulting estimate of the $\dot{V}_A/\dot{Q}$ distribution. Inert gases are the tracer gases of choice." (Olszowka and Wagner, 1980) (p. 284.)

(A list of abbreviations used in the following text is given in Appendix A, p. 1595.)

THE MULTIPLE INERT GAS METHOD

The multiple inert gas method, based upon inert gas retention (and the almost identical excretion) equations (Farhi, 1967) and individually measured solubilities, uses a computer to determine the $\dot{V}_A/\dot{Q}$ distributions. The "retention" of an inert gas tracer is essentially the proportion of the mixed venous concentration remaining in the arterial blood after a single pass through the lungs. The present paper starts by presenting a detailed derivation of the retention equations (starting from basic physicochemical principles and using elementary algebra) for any predicated $\dot{V}_A/\dot{Q}$ distribution. Following is a discussion of how those equations may be used in the inverse sense; that is, finding the $\dot{V}_A/\dot{Q}$ distribution if the retentions and solubilities are known. Next, certain of the published results in the multiple inert gas method literature are examined to enable a better understanding of the characteristics of that methodology. Then by means of computer "experiments", the limits of resolution attainable by the method are probed. Finally, $\dot{V}_A/\dot{Q}$ distributions estimated by the method are compared with distributions estimated by the use of oxygen, carbon dioxide, pH and haemodynamic variables.

Solubility, Retention and Ventilation–Perfusion

Single compartment

Consider a bottle containing n litre of blood and V litre of air, both n and V unknown, with some initial concentration of tracer inert gas in the blood and, initially, no tracer in the air. The ratio of air to blood (F) in the bottle can be determined if the *solubility* of the tracer gas in blood is known, or separately measured, and if the concentration of tracer *retained* in the blood (or the final concentration in the gas phase after prolonged vigorous shaking) is measured.

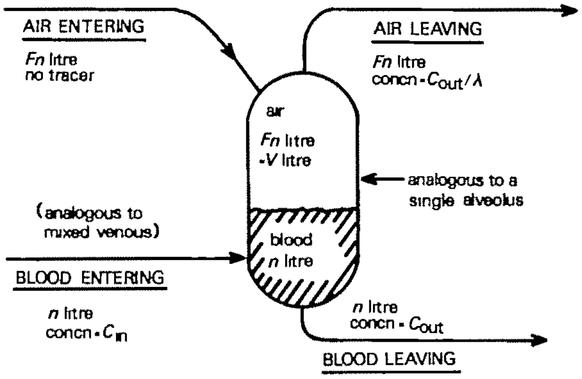

FIG. 1. Single compartment with $\dot{V}_A/\dot{Q} = F$. Retention (R) $= C_{out}/C_{in}$. If $\dot{n} = \dot{Q}$, then $\dot{V}_A = \dot{n}F$.

Inert gas solubility. At any given temperature, a non-reactive tracer gas contained in a volume of blood in equilibrium with a volume of gas will divide itself between the gas phase and the liquid phase so that:

$$\frac{\text{concentration of tracer gas in the blood}}{\text{concn of tracer gas in the gas phase}} = \lambda$$

This ratio, λ, is the Ostwald solubility coefficient, also called the "blood:air ratio" or the "partition coefficient". The concentration may be thought of as the number of molecules of tracer gas per litre of blood, or per litre of gas, or per litre of space, etc. A convenient concentration "unit" for these purposes is ml of tracer gas (STPD) per litre. The amount of tracer gas contained in a volume of blood is the product of the volume of blood and the tracer gas concentration. In n litre of blood of concentration C_t of tracer gas, the number of ml (STPD) of tracer gas $= nC_t$.

Retention. The retention refers to the ratio of the final and initial tracer gas partial pressures (concentrations) in blood when blood:air partitioning to equilibrium has occurred. In the bottle model of figure 1, let $F = V/n$. We use F instead of $\dot{V}_A/\dot{Q}$ to simplify the equations. After the bottle has been shaken (at body temperature) for a long time, the tracer gas is partitioned (and equilibrated) between the blood and the air. The

TABLE I. *Approximate solubilities and infusion rates of tracer gases*

Tracer gas	Approximate solubility (λ)	Approx. (gas phase) tracer delivered in 5-ml min^{-1} infusion (ml min^{-1})
Sulphur hexafluoride	0.0076	$0.003 = \alpha_1$
Ethane	0.092	$0.10 = \alpha_2$
Cyclopropane	0.415	$0.20 = \alpha_3$
Halothane	2.3	$2.0 = \alpha_4$
Ethyl ether	11.7	$2.0 = \alpha_5$
Acetone	200	

final concentration of tracer in the blood is C_{out} ml litre^{-1}. By the definition of λ, the final concentration in the air is C_{out}/λ ml litre^{-1}. The total amount of tracer originally in the blood was nC_{in} ml. This is now partitioned between the blood and the air:

$$nC_{\text{in}} = nC_{\text{out}} + nF(C_{\text{out}}/\lambda) = nC_{\text{out}}(1+F/\lambda) \quad (1)$$

$$C_{\text{out}} = C_{\text{in}}/(1+F/\lambda) \quad (2)$$

This may be extended to a dynamic situation by imagining that the bottle is filled and emptied once each 1 min. Thus, the n litre of blood may be thought of as $\dot{n}$ litre min^{-1}.

Starting with equation (2) (without knowing either n or the original amount of tracer gas added), if retention (R) and λ are measured:

$$C_{\text{out}}/C_{\text{in}} = 1/(1+F/\lambda) = R \quad (3)$$

$$RF/\lambda = 1-R \quad (4)$$

$$F = \lambda/R - \lambda \quad (5)$$

With one compartment and one tracer gas, the $\dot{V}$A/$\dot{Q}$ of that compartment (all the blood, $\dot{n}$ litre min^{-1}, goes to the single compartment) is uniquely determined.

Multiple compartments

However, with multiple $\dot{V}$A/$\dot{Q}$ compartments, C_{out} cannot be directly measured at each alveolus, so that equation (3) cannot be used. Expressions relating the perfusion and $\dot{V}$A/$\dot{Q}$ of each compartment to the arterial (mixed alveolar effluent) concentrations must be developed.

Administration of inert gases. A multiple inert gas method $\dot{V}$A/$\dot{Q}$ distribution estimation is initiated by infusing i.v., at some constant rate (say 5 ml min^{-1}), a solution of six inert gases of widely varying solubility, dissolved in normal saline. The tracer gases chosen, and their approximate blood:gas partition coefficients are detailed in table I.

Measurements made. Samples of arterial blood and mixed venous blood taken after about 20 min of the infusion are each equilibrated successively with two aliquots of fresh air. The four resulting gas phase samples are analysed in a gas chromatograph to obtain relative tracer gas concentrations. The expirate, mixed in a heated non-absorptive chamber, is analysed similarly. The solubilities and retentions are computed from these six sets of measurements. The exhaled minute volume ($\dot{V}$E litre min^{-1}) is also measured. Simultaneous determination of cardiac output is made, as is estimation of deadspace ($\dot{V}$D) by independent means.

Theory of analytical approach. Assume that the exhalation comes from two kinds of places: (1) deadspace, where the exhalation has not come into contact with blood (its $\dot{V}$A/$\dot{Q}$ is "infinite"); (2) perfused alveoli, where the effluent exhalation has reached perfect equilibrium with the blood perfusing each alveolus.

Assume that the mixed venous blood goes to two kinds of places: (1) the perfused alveoli just mentioned, and (2) directly to the pulmonary vein without ever having come into contact with air; this is "shunt"; its $\dot{V}$A/$\dot{Q}$ is zero.

Shunt, as it is used with respect to respired gases, must be distinguished from the shunt involved in inert gas measurements. A (small) fraction of the oxygenated blood is used to satisfy the metabolic requirements of pulmonary and cardiac tissue before entering the arterial system. While (after equilibration) this would not affect the tracer gas concentrations in the arterial blood, it changes a portion of what would be arterial blood into the equivalent of venous blood, with substantial effect upon the arterial oxygen tension at high inspired oxygen tensions. This effect on arterial metabolic gas tensions is indistinguishable from actual shunt in the lung, where mixed

TABLE II. *$(\dot{V}A/\dot{Q})$ and log $(\dot{V}A/\dot{Q})$ values for calculated compartments. A: Forty-three compartments used in this exposition. Each compartment is 25.9% greater, or 20.6% less than its next neighbour. B: Fifty compartments used in multiple inert gas method (MIGM) literature. Each compartment is 23.5% greater, or 19.0% less than its next neighbour*

Compartment No. (j)	A: Present study		B: MIGM literature	
	$(\dot{V}A/\dot{Q})_j$	$\log(\dot{V}A/\dot{Q})_j$	$(\dot{V}A/\dot{Q})_j$	$\log(\dot{V}A/\dot{Q})_j$
0	0	—	0	—
1	0.01	−2	0.005	−2.30103
2	0.01259	−1.9	0.00617	−2.20952
3	0.01585	−1.8	0.00762	−2.11801
4	0.01995	−1.7	0.00941	−2.02650
5	0.02512	−1.6	0.01162	−1.93498
6	0.03162	−1.5	0.01434	−1.84347
7	0.03981	−1.4	0.01770	−1.75196
8	0.05012	−1.3	0.02185	−1.66045
9	0.06310	−1.2	0.02698	−1.56894
10	0.07943	−1.1	0.03331	−1.47743
11	0.1	−1	0.04112	−1.38592
12	0.1259	−0.9	0.05076	−1.29441
13	0.1585	−0.8	0.06268	−1.20289
14	0.1995	−0.7	0.07738	−1.11138
15	0.2512	−0.6	0.09553	−1.01987
16	0.3162	−0.5	0.11793	−0.92836
17	0.3981	−0.4	0.14590	−0.83685
18	0.5012	−0.3	0.17975	−0.74534
19	0.6310	−0.2	0.22191	−0.65383
20	0.7943	−0.1	0.27396	−0.56232
21	1	0	0.33822	−0.47080
22	1.259	0.1	0.41755	−0.37929
23	1.585	0.2	0.51549	−0.28778
24	1.995	0.3	0.63640	−0.19627
25	2.512	0.4	0.78567	−0.10476
26	3.162	0.5	0.96996	−0.01325
27	3.981	0.6	1.19747	0.07826
28	5.012	0.7	1.47834	0.16977
29	6.310	0.8	1.82510	0.26129
30	7.943	0.9	2.25319	0.35280
31	10	1.0	2.76169	0.44431
32	12.59	1.1	3.43415	0.53582
33	15.85	1.2	4.23966	0.62733
34	19.95	1.3	5.23410	0.71884
35	25.12	1.4	6.46180	0.81035
36	31.62	1.5	7.97746	0.90186
37	39.81	1.6	9.84863	0.99338
38	50.12	1.7	12.15870	1.08489
39	63.10	1.8	15.01062	1.17640
40	79.43	1.9	18.53147	1.26791
41	100	2.0	22.87816	1.35942
42	“infinite”		28.24440	1.45093
43			34.86933	1.54244
44			43.04819	1.63395
45			53.14546	1.72547
46			65.61112	1.81698
47			81.00069	1.90849
48			100	2.0
49			“infinite”	

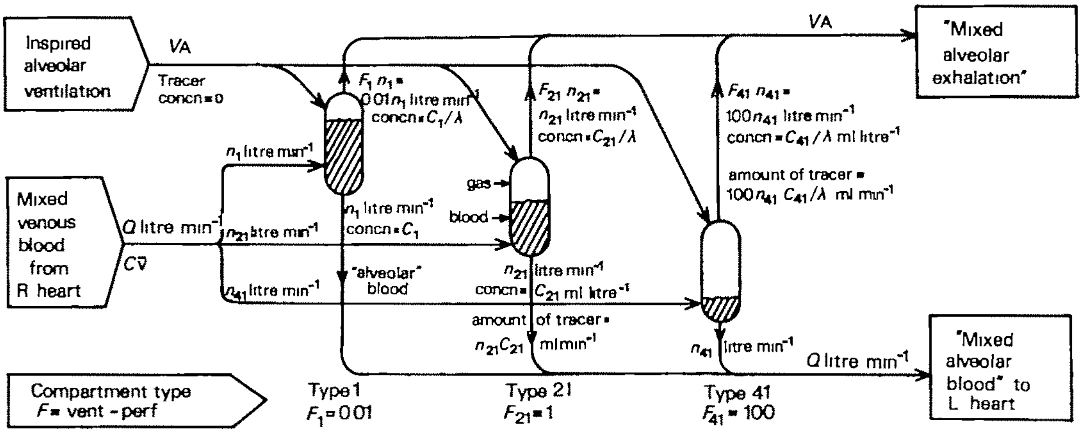
Inspired alveolar ventilation
VA
Tracer concn = 0
$F_1 n_1 =$ 0·01n_1 litre min^{-1} concn = C_1/λ
n_1 litre min^{-1}
$F_{21} n_{21} =$ n_{21} litre min^{-1} concn = C_{21}/λ
$F_{41} n_{41} =$ 100n_{41} litre min^{-1} concn = C_{41}/λ ml litre^{-1}
amount of tracer = 100n_{41} C_{41}/λ ml min^{-1}
VA
"Mixed alveolar exhalation"
Mixed venous blood from R heart
Q litre min^{-1}
$C\bar{v}$
n_{21} litre min^{-1}
n_{41} litre min^{-1}
n_1 litre min^{-1} concn = C_1
"alveolar" blood
gas
blood
n_{21} litre min^{-1} concn = C_{21} ml litre^{-1}
amount of tracer = $n_{21}C_{21}$ ml min^{-1}
n_{41} litre min^{-1}
Q litre min^{-1}
"Mixed alveolar blood" to L heart
Compartment type F = vent - perf
Type 1 F_1 = 0·01
Type 21 F_{21} = 1
Type 41 F_{41} = 100

FIG. 2. An imaginary lung without deadspace, containing only three types of compartment for ease of demonstration and using only one tracer gas. If the $\dot{V}_A/\dot{Q}$ of a compartment were 0 (shunt) the exhaled "alveolar" concentration of that component would be 0, and the concentration of the blood leaving would be equal to $C\bar{v}$. "Mixed alveolar exhalation": at equilibrium contains all the added tracer flow = α ml min^{-1}; otherwise, contains $\dot{n}(C\bar{v}-Ca)$ ml min^{-1}.

venous blood passes through the lung without exposure to ventilation.

Undoubtedly, there is a continuum of alveolar $\dot{V}_A/\dot{Q}$ types. However, for ease of exposition, and because digital computers abhor continua, it is assumed that there exist in the lungs of a subject 43 types of alveolus (table II). In each of these types, there is a specified $\dot{V}_A/\dot{Q}$. (The literature on multiple inert gas methodology uses 50 compartments.) The postulated ventilation–perfusion compartment types are spaced logarithmically evenly (because that is the only practical way to present a variable which extends over a range of more than 10000:1) at 0.1 $\log_{10}$ units. The range from $\dot{V}_A/\dot{Q} = 0.01$ to 100 is then covered by 41 compartments, which are augmented by shunt and deadspace for a total of 43. Assume that these are the only types of alveoli. This means, for example, that, in the No. 21 compartment, each 1 ml of perfusing blood is equilibrated with 1 ml of air (or gas) before exhalation occurs. In the No. 1 type, only 0.01 ml of air is equilibrated with 1 ml of blood. In the No. 41 compartment, $\dot{V}_A/\dot{Q} = 100$; 100 ml of air is equilibrated with 1 ml of blood. Shunt and deadspace also occur outside alveoli.

Assumptions. (1) The tracer gases are inert; that is, the solubility curve in blood is linear, with no hysteresis.

(2) Perfect mixing of the infused tracer gases with the blood before entering the lung.

(3) Perfect mixing of alveolar effluent blood to form a uniform Ca before entering the arterial tree.

(4) Only fresh (no tracer content) inhalation gas enters the alveolus. This is an obvious oversimplification, not only because the deadspace contents are inhaled, but because all the alveoli do not empty synchronously, so that the returning air from the deadspace is not evenly distributed.

(5) That equilibrium has been reached. At least two kinds of equilibrium are involved. Equilibrium of the respiratory tissue, and equilibrium within each alveolus of the gas with the blood effluent.

Multiple compartment analysis

Referring to figure 2, assume that during the course of each breath (at equilibrium):

(a) The blood perfusing the alveolus entered as mixed venous blood with $C\bar{v}$ concentration of tracer gas, and leaves at a concentration C_j determined by the amount of air with which it equilibrates, where j refers to the particular $\dot{V}_A/\dot{Q}$ "compartment" (the lumped aggregate of all alveoli having that particular $\dot{V}_A/\dot{Q}$ value).

(b) Before the exhalation of the breath under consideration, equilibrium (in each alveolus) has occurred. At equilibrium the tracer concentration in the alveolar air is equal to the concentration in blood leaving the alveolus divided by λ.

The basic relationships governing this system are:

I. All of the alveolar blood volumes, each 1 min ($\dot{n}$) from each type of compartment, contribute their tracer gas content to make up the final arterial (mixed alveolar) blood:

$$\dot{n}_1C_1+\dot{n}_{21}C_{21}+\dot{n}_{41}C_{41} = Ca\dot{Q}. \qquad (6)$$

(Note that there will be as many equations of this kind as there are tracer species.)

Equation (6) contains alveolar blood concentrations, each of which we cannot measure, but which mix together to form the arterial blood.

II. Concerning the tracer gas in each alveolus, what comes in must go out, and *vice versa*. For each compartment the product of the volume of blood entering and its concentration equals the product of the blood volume leaving and its concentration plus the product of the air volume leaving and its concentration. For compartment No. 1, remembering the exhaled alveolar concentration is C_1/λ:

$$\dot{n}_1C\bar{v} = \dot{n}_1C_1+F_1\dot{n}_1C_1/\lambda \qquad (7)$$

(Remember $F = \dot{V}\text{A}/\dot{Q}$)

Dividing both sides by n_1, and factoring out C_1 from the right side:

$$C\bar{v} = C_1(1+F_1/\lambda)$$

$$C_1 = C\bar{v}/(1+F_1/\lambda) \qquad (8)$$

(representative of all other compartments)

Substituting into equation (6):

$$\dot{n}_1C\bar{v}/(1+F_1/\lambda)+\dot{n}_{21}C\bar{v}(1+F_{21}/\lambda)+\dot{n}_{41}C\bar{v}(1+F_{41}/\lambda) = Ca\dot{Q} \qquad (9)$$

Factoring out $C\bar{v}$, and remembering $Ca/C\bar{v} = R$:

$$\frac{\dot{n}_1}{1+0.01/\lambda}+\frac{\dot{n}_{21}}{1+1/\lambda}+\frac{\dot{n}_{41}}{1+100/\lambda} = R\dot{Q} \qquad (10)$$

(Note that there are as many of these equations as there are tracer species.)

III. The sum of all the alveolar blood volumes (each minute) from all compartments is equal to the cardiac output:

$$\dot{n}_1+\dot{n}_{21}+\dot{n}_{41} = \dot{Q} \qquad (11)$$

Going back to the diagram in figure 2:

$$F_1\dot{n}_1+F_{21}\dot{n}_{21}+F_{41}\dot{n}_{41} = \dot{V}\text{A} \qquad (12)$$

Shortened terminology and symbology. If equation (12) represented a lung with all 41 types of compartments there would be 41 terms on the left. To condense this, a "shorthand" notation is utilized.

Designate the products (Fn) as F_jn_j where j is any number from 0 to 41.

Designate the operation: "add together all values of the following" as Σ, "the sum of", so that $\Sigma\, F_jn_j = \dot{V}\text{A}$ could be used instead of equation (12).

We specify the range of values of j applicable to the specific problem by annotating the capital sigma thus:

$$\sum_{j=0}^{j=41}$$

which is to say: "the sum of j; from, and including, $j = 0$, to, and including, $j = 41$" (or: "the sum of 42 terms in each of which j is assigned a number starting with 0, going through all the intervening numbers, and ending with 41"), giving a "shorthand" equation:

$$\sum_{j=0}^{j=41} F_j\dot{n}_j = \dot{V}\text{A} \qquad (13)$$

The sum of the alveolar minute ventilations from all compartments is $\dot{V}\text{A}$. In this notation, equation (10) becomes:

$$\sum_{j=0}^{j=41} \dot{n}_j/(1+F_j/\lambda) = R\dot{Q} \qquad (14)$$

Equation (14) can be written for each tracer gas. To designate this we use a subscript "i" to denote each gas. For example, let SF_6 be denoted by $i = 1$. Then λ_i becomes the partition coefficient of SF_6 when i is assigned the value 1. Similarly Ca_i is the arterial concentration of gas i, and $C\bar{v}_i$ is the mixed venous concentration of gas i.

Equation (14) now may be written:

$$\sum_{j=0}^{j=41} \dot{n}_j/(1+F_j/\lambda_i) = R_i\dot{Q} \qquad (15)$$

Note that those variables with subscripts j are the same for all the gases. The value of those variables with subscripts i are different for each gas. Those without any subscripts are the same wherever they may be.

It is convenient to use the *fraction* of the cardiac output, $\dot{Q}_j$, going to each compartment, rather than the volume of blood per minute $(\dot{n}_j)$.

Since $\quad \dot{Q}_j = \dot{n}_j/\dot{Q},\ \dot{n}_j = \dot{Q}\dot{Q}_j \qquad (16)$

equations (11) and (15) become equations (17) and (18), respectively:

$$\sum_{j=0}^{j=m} \dot{Q}_j = 1 \tag{17}$$

$$R_i = \sum_{j=0}^{j=m} \dot{Q}_j/(1+F_j/\lambda_i) \tag{18}$$

where m represents the maximum number of non-shunt compartments.

HOW THE EQUATIONS ARE USED

Equations (17) and (18) may be used in three ways:

First, if the set of $(\dot{Q}_j, F_j)$ points are predicated (that is, a distribution postulated), the corresponding R_i may be calculated. Note that from any (even very large) number of $(\dot{Q}_j, F_j)$ pairs, a set of R_i may be straightforwardly calculated. (The inverse operation, going from a set of R_i to the distribution, is not straightforward.)

Second, a set of $(\dot{Q}_j, F_j)$ is "inferred", or estimated, from a much smaller set of (R_i, λ_i) by a complicated computerized method. Thus many points (say 49) on a $\dot{V}_A/\dot{Q}$ distribution curve ($\dot{Q}_j$ *v.* F_j) are "derived" from a set of determinations of R_i and λ_i by the multiple inert gas method computer program (Wagner, Salzman and West, 1974).

Third, we have found that a two-compartment plus shunt distribution, which we name a "tripartite" distribution, may be found, which "matches" any postulated distribution, no matter how detailed. By "matches" is meant, that each pair of R_i, calculated from each of the "matching" distributions, are the same within the expected percent error of actual determination of the R_i and λ_i. Every distribution tested has been matched by a unique tripartite distribution. Since it is plausible that there is always at least some small amount of shunt in every lung, and since there is no method by which the *actual* shunt may be measured, it seems logical always to include the shunt compartment (which sometimes turns out to have no perfusion). Sometimes, a shunt and one alveolar compartment ("bipartite") distribution matches the set of (R_i, λ_i). In that case, there is an infinitude of matching tripartite solutions. Of course, the true distribution is certainly not this tripartite distribution; nor can it be determined by the multiple inert gas method or, indeed, by any extant methodology, to our knowledge.

Calculation of unknown variables from measured R *and* λ

Extending the previously developed process for ascertaining the $\dot{V}_A/\dot{Q}$ of a single compartment using a single tracer gas to plural compartments, consider the situation where there are two compartments, one of which is shunt ($F_o = 0$).

Let F_1 be the $\dot{V}_A/\dot{Q}$ of the other compartment. Let $\dot{Q}_o$ be the fraction of the cardiac output going to shunt, and $\dot{Q}_1$ the fraction going to the other compartment. Use two tracer gases, ethane and halothane. Equation (17) becomes:

$$\dot{Q}_o + \dot{Q}_1 = 1 \tag{19}$$

Equation (18) becomes (for ethane, using nominal solubilities):

$$\dot{Q}_o + \dot{Q}_1/(1+F_1/\lambda\ \text{eth}) = R\ \text{eth}$$

$$\dot{Q}_o + \dot{Q}_1/(1+F_1/0.092) = R\ \text{eth} \tag{20}$$

and for halothane:

$$\dot{Q}_o + \dot{Q}_1/(1+F_1/2.3) = R\ \text{hal} \tag{21}$$

Calculated example. (Algebraic and arithmetic details are presented in Appendix B.) Equations (19), (20) and (21) are independent, and contain three unknowns: $\dot{Q}_o$, $\dot{Q}_1$ and F_1. Suppose the measured values of λ and R are: R eth $= 0.38947$; λ eth $= 0.092001$; R hal $= 0.79810$; λ hal $= 2.30004$ (note that in the literature pertaining to the multiple inert gas method, analytical results are reported to 6 decimal places).

The solution is:

$$F_1 = 0.999,\ \dot{Q}_1 = 0.6667,\ \dot{Q}_o = 0.3333$$

These are the specifiers of a bipartite distribution.

Suppose the F values of both compartments were initially unknown, that is, it is not assumed that one compartment is shunt. Equation (17) becomes:

$$\dot{Q}_1 + \dot{Q}_2 = 1 \tag{22}$$

Equation (18) becomes (for ethane):

$$\dot{Q}_1/(1+F_1/\lambda\ \text{eth}) + \dot{Q}_2/(1+F_2/\lambda\ \text{eth}) = R \tag{23}$$

and for halothane:

$$\dot{Q}_1/(1+F_1/\lambda\ \text{hal}) + \dot{Q}_2/(1+F_2/\lambda\ \text{hal}) = R \tag{24}$$

Thus there are three equations and four unknowns.

Solution of equations. To solve these equations, start by selecting a definite value for F_2, and substituting it into equations (23) and (24). This

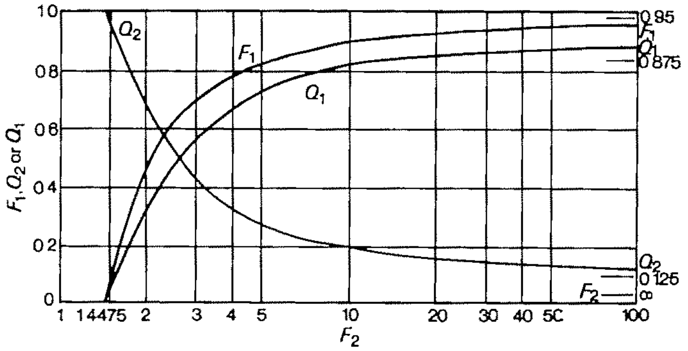

FIG. 3. Infinitude of solutions of retention equations (23) and (24) for a model with two compartments (neither shunt) and two tracer gases. For example, along the vertical line drawn through $F_2 = 10$: $\dot{Q}_2 = 0.18$, $\dot{Q}_1 = 0.8$ and $F_1 = 0.9$.

reduces the "unknowns" to three, "temporarily", and allows for a definite solution.

Algebraic and arithmetic details of carrying out the algebra to develop easily usable formulae are presented in Appendix C. Suppose it has been experimentally determined that: R enf = 0.08333, λ enf = 0.100000, R hal = 0.61111 and λ hal = 2.20000.

Starting with $F_2 = 0.5$, inserting these values to equation (30) (Appendix C) produces:

$$F_1 = 2.000;\ \dot{Q}_1 = 0.800;\ \dot{Q}_2 = 0.300.$$

These results may be confirmed by inserting them to equations (23) and (24).

Now assume a new value for F_2: let $F_2 = 0.4$, and exercise equations (30), (29) (Appendix C) and (24). Results are:

$$F_1 = 1.809;\ \dot{Q}_1 = 0.79;\ \dot{Q}_2 = 0.21,$$

another set of values yielding the same retentions when substituted into equation (18). Continuing in the same way, sets of values which yield the same retentions are presented by graph in figure 3, showing values of F_1, $\dot{Q}_1$ and $\dot{Q}_2$ *v.* F_2. Conclusion: to find two compartments unequivocally, at least three tracer gases are required.

In general, using this type of analysis, three unknown compartments may be found by using five tracer gas species. Because, in a real lung, we always expect some shunt and, therefore, the $\dot{V}\text{A}/\dot{Q}$ of one compartment is assumed to be zero, it would appear that three compartments might be found using four tracer gas species of widely varying values of λ.

Retention v. *solubility curves*

When a set of (R_i, λ_i) is measured during an experiment, or when a set is calculated for any given predicated distribution ($\dot{Q}_j$, F_j and λ_j) and plotted as log R_i *v.* log λ_i, the points always fall on a smooth monotonic curve (fig. 4). This curve is uniquely characterized by the $\dot{V}\text{A}/\dot{Q}$ distribution from which it was derived. However, not every smooth monotonic curve of log R *v.* log λ is representative of a distribution. An interesting observation is that after five or six points covering the complete range of log λ are placed on a graph, all the smooth, monotonic curves which may be drawn through those points differ insignificantly from one another, providing an indication that using more tracer gases would not really provide more information about the distribution (fig. 5).

Relation between retention and distribution

The "forward operation". Figures 4 and 5 illustrate the "forward" and "inverse" relationship between the $\dot{V}\text{A}/\dot{Q}$ "distribution", and the R_i. The operation, which starts with the predicated $\dot{V}\text{A}/\dot{Q}$ distribution and calculates the retentions for each value of λ is named "forward" because it is a straightforward set of calculations. A predicated distribution may be continuous (that is, have an infinite number of compartments) since it is imagined, not measured.

The calculated curve of R *v.* λ may also be as continuous as desired. Equation (18) may be restated:

$$R(\lambda) = \sum \frac{\dot{Q}_j}{1 + F_j/\lambda} \qquad (25)$$

"$R(\lambda)$", emphasizing that R is a function of λ. (It is to be read as "R of lambda", and does NOT mean "R times λ").

The "inverse" operation. The determination of

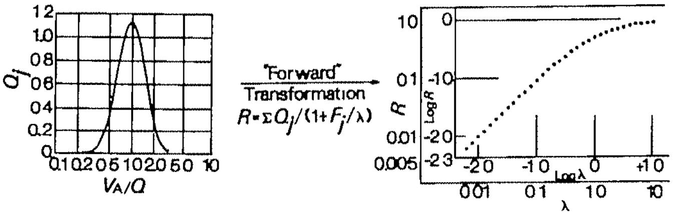

FIG. 4. The straightforward development of the unique R v. λ curve from a representative (known) distribution.

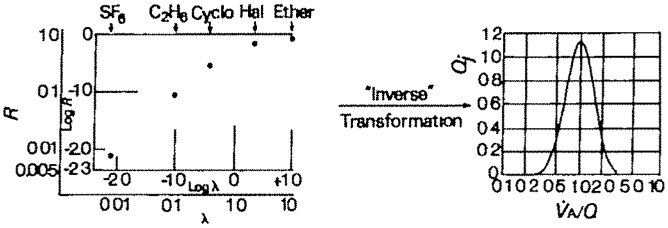

FIG. 5. The "inverse" process of deriving the $\dot{V}_A/\dot{Q}$ distribution starting with a "measured" (calculated from tonometry measurements) set of retentions and λ.

the "distribution", $\dot{Q}_j$ v. log F_j starting with a "given" curve of R v. λ is not straightforward. There is no analytical expression for $\dot{Q}_j$. The $\dot{Q}_j$ values are determined by an iterative procedure. First, equation (18) is applied to some proposed initial distribution. The resulting set of (R_i, λ_i) is compared with the "given" curve, and an error function is defined. This error function may be chosen to be the weighted sum of squares of the percentage errors or the weighted sum of the absolute error percentages. The weights are chosen to be roughly inversely proportional to the expected percentage error in the actual *in vivo* measurement of each tracer. For instance, the percentage error of the retention of acetone is much less than in the other retentions, because it is not measured directly, but is estimated from the mixed expirate acetone relative concentration (Wagner, Salzman and West, 1974).

A small change (perturbation) in one of the distribution specifiers (one of the $\dot{Q}_j$ or F_j) is then made. The value of the resulting error function is compared with the preceding error function value. If the error function value has decreased, additional perturbations in the same direction are made; if the error function value has increased, a reversal of the perturbation direction is indicated. Such perturbations are successively applied to each of the distribution variables until a minimum error function is reached, or until error less than the expected errors of *in vivo* determination is reached.

PRACTICAL APPLICATIONS

The preceding concepts may be applied to published data (Wagner et al., 1978). Tables 1 and 2 of that paper (Wagner et al., 1978) contain cardiac output, retention and inert gas solubility data, while their associated figures 1 and 3 present $(\dot{V}_A/\dot{Q})$ distribution curves for seven patients. Restricting the analysis to the *perfusion* distribution, acetone, which has such high solubility that it relates insignificantly to the perfusion distribution, may be disregarded.

Methods I

(a) A measuring microscope directly viewing the published figure 1 (Wagner et al., 1978) was used to measure the ordinate (perfusion distances). The corresponding abscissa values were selected from the list of allowed values in table IIB.

(b) The ordinate value of each point on the curve was then calculated by comparing with the figure calibrations. The accuracy was tested by comparing their sum with the published values of cardiac output. The $\dot{Q}_j$ values were then determined by dividing each compartmental perfusion by the sum of perfusions.

(c) Inserting these point-by-point values to a set of equations similar to equation (18) (the difference being that the compartments have $\dot{V}_A/\dot{Q}$ values in the table IIB series) a set of values

PUBLISHED TABLES

TABLE III. *Details of extracting* R *values from published perfusion distribution curves for first patient* (*Wagner et al., 1978*) (*W78*)

Compartment No. (j)	F_j	Measured ordinate (in.)	Divide by 13.107 because 19.66 in. = 1.5 litre min^{-1} "measured" $\dot{Q}_j \times$ CO	Multiply each value by 0.98 to correct total to published CO (cardiac output)	Divide each value by the CO $\dot{Q}_j$	SF$_6$ coefficient: $\frac{0.00495}{F_j+0.00495}$	Multiply by $\dot{Q}_j$	Ethane coefficient: $\frac{0.07778}{F_j+0.07778}$	Multiply by $\dot{Q}_j$
1	0	n/a	n/a	n/a	0.0400	1	0.04	1	0.04
2	0.222	0.32	0.024	0.0235	0.00373	0.0218	0.00008	0.2595	0.000968
3	0.274	2.86	0.218	0.2136	0.0339	0.01775	0.00060	0.2211	0.0075
4	0.338	9.47	0.723	0.7085	0.1125	0.01443	0.001624	0.1871	0.02105
5	0.418	14.80	1.129	1.1063	0.1756	0.01171	0.002055	0.1569	0.02755
6	0.515	17.13	1.307	1.2807	0.2033	0.00952	0.001935	0.1312	0.02668
7	0.636	17.02	1.299	1.2729	0.202	0.007723	0.00156	0.10897	0.02201
8	0.786	12.74	0.972	0.9525	0.1512	0.006258	0.000946	0.09	0.01361
9	0.970	6.11	0.466	0.4566	0.0725	0.005077	0.000368	0.0742	0.00538
10	1.197	0.44	0.034	0.0333	0.0053	0.00412	0.00002	0.06101	0.00032
		80.89 in. total = 96% of CO	6.172 litre min^{-1} total. 2% error		1.000 total		0.0492 total = extracted R_{SF_6} = 103.2% of W78		0.1651 total = extracted *R*eth = 113% of W78

Compartment No. (j)	Cyclopropane coefficient: $\frac{0.50197}{F_j+0.50197}$	Multiply by $\dot{Q}_j$	Halothane coefficient. $\frac{2.18463}{F_j+2.18463}$	Multiply by $\dot{Q}_j$	Ether coefficient: $\frac{10.8171}{F_j+10.8171}$	Multiply by Q_j
1	1	0.04	1	0.04	1	0.04
2	0.6934	0.002586	0.9078	0.00339	0.9799	0.00365
3	0.6469	0.02193	0.8886	0.03012	0.9753	0.03306
4	0.5976	0.06723	0.866	0.09743	0.9697	0.1091
5	0.5456	0.09581	0.8394	0.1474	0.9628	0.16907
6	0.4936	0.10035	0.8092	0.1645	0.9546	0.19406
7	0.4411	0.0891	0.7745	0.1565	0.9445	0.19078
8	0.3897	0.05893	0.7354	0.1112	0.9323	0.14096
9	0.34102	0.02472	0.6925	0.0502	0.9177	0.0665
10	0.2955	0.00156	0.646	0.0034	0.90037	0.0048
		0.5022 total = Extracted *R* cyclo = 111.9% of W78		0.804 total = Extracted *R* hal = 104.3% of W78		0.952 total = Extracted *R* ether = 100.9% of W78

TABLE IV. *Details of extracting* R *from published perfusion distribution curves for third patient* (*Wagner et al., 1978*) (*W78*)

Compartment No. (j)	F_j	Measured ordinate (in.)	Divide by 6.072 to obtain (litre min^{-1}) "measured" $\dot{Q}_j \times$ CO	Divide each value by the CO $\dot{Q}_j$	SF$_6$ coefficient: $\frac{0.00848}{F_j+0.00848}$	Multiply by $\dot{Q}_j$	Ethane coefficient: $\frac{0.08838}{F_j+0.08838}$	Multiply by $\dot{Q}_j$
1	0.0411	0.45	0.074	0.0127	0.171	0.002172	0.6826	0.008669
2	0.0508	1.27	0.209	0.0359	0.143	0.005135	0.635	0.0228
3	0.0627	1.65	0.272	0.0468	0.1191	0.005575	0.585	0.02738
4	0.0774	0.965	0.159	0.0274	0.09874	0.002706	0.5331	0.01461
5	0.97	0.33	0.054	0.00928	0.008667	0.0000804	0.0835	0.000775
6	1.197	2.31	0.38	0.0653	0.007035	0.000459	0.06876	0.00449
7	1.478	4.91	0.809	0.139	0.005705	0.000793	0.0564	0.007843
8	1.825	6.34	1.044	0.1795	0.004625	0.0008302	0.04619	0.008291
9	2.253	6.4	1.054	0.1812	0.00375	0.000679	0.03775	0.00684
10	2.782	5.18	0.853	0.1467	0.003039	0.000446	0.03079	0.004517
11	3.434	3.51	0.579	0.0996	0.002463	0.000245	0.02509	0.002499
12	4.24	1.55	0.255	0.0438	0.001996	0.0000874	0.02042	0.000894
13	5.234	0.45	0.074	0.0127	0.0016176	0.0000205	0.01661	0.000211
			Total 5.816 litre min^{-1} CO +5.7% "error"	0.9999 total		Total = 0.0192 = Extracted RSF$_6$ = 279% of W78		Total = 0.1098 = Extracted Reth 137% of W78

Compartment No. (j)	Cyclopropane coefficient: $\frac{0.55146}{F_j+0.55146}$	Multiply by $\dot{Q}_j$	Halothane coefficient: $\frac{2.67246}{F_j+2.67246}$	Multiply by $\dot{Q}_j$	Ether coefficient: $\frac{12.49269}{F_j+12.49269}$	Multiply by $\dot{Q}_j$
1	0.9306	0.01182	0.98485	0.012507	0.99672	0.01266
2	0.9157	0.03287	0.981346	0.03523	0 99595	0.035755
3	0.8979	0.04202	0.97708	0.045727	0.995006	0.04657
4	0.8769	0.024028	0.97185	0.026629	0.99384	0.02723
5	0.36245	0.003364	0.7337	0.006809	0.92795	0.00861
6	0.3154	0.0206	0.69065	0.0451	0.91256	0.05959
7	0.2717	0.03777	0.6439	0.0895	0.8942	0.12429
8	0.23205	0.041653	0.5942	0.10666	0.8725	0.15662
9	0.19664	0.03563	0.5426	0.09832	0.84721	0.1535
10	0.16543	0.02427	0.48996	0.07188	0.8179	0.11998
11	0.13837	0.01378	0.4376	0.04359	0.7844	0.078125
12	0.11509	0.005041	0.3866	0.01693	0.7466	0.0327
13	0.0953	0.00121	0.338	0.00429	0.7047	0.00895
		Total = 0.294 = Extracted Rcyclo. = 129% of W78		Total = 0.6027 = Extracted Rhal = 113% of W78		Total = 0.865 = Extracted Rether = 103% of W78

TABLE V. *Percent difference of extracted* R *from published* R (*Wagner et al., 1978*) *for asymptomatic asthmatic patients*

Patient No.	SF_6	Ethane	Cyclopropane	Halothane	Ether
1	+3	+8	+12	+5	+1
2	+25	0	−3	0	0
3	+179	+37	+29	+13	+3
4 (control)	+41	−6	+4	−1	0
5	+26	−1	+2	+2	0
6	+42	+14	+11	+6	+4
7	+59	+10	+13	+6	+2

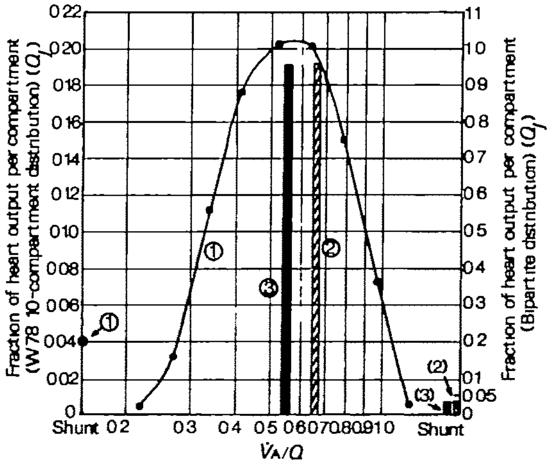

FIG. 6. (1) Wagner and colleagues' (1978) (W78) published curve for patient No. 1 with ordinate converted to fractional perfusion per compartment (large dots with connecting line). (2) Cross-hatched bars designate the unique bipartite distribution yielding R values indistinguishable from the published R. (3) Black bars are the bipartite distribution derived from the extracted R.

of R was calculated straightforwardly. We named these R values the "extracted R".

(d) Details of the process as applied to the patients (Nos 1, 3) studied by Wagner and colleagues are presented in tables III and IV. The extracted R values sometimes differed markedly from the published values (Wagner et al., 1978) (table V).

Methods II

To find the tripartite (or bipartite) distribution:

(a) Assume some initial set of (trial) values of $\dot{Q}_o$, $\dot{Q}_1$, F_1 and F_2 ($\dot{Q}_2 = 1-\dot{Q}_o-\dot{Q}_1$).

(b) Use the values of λ provided by Wagner and colleagues (1978).

(c) Insert these to equation (18) (j now runs from 0 to 2); there are five equations analogous to:

$$\frac{\dot{Q}_o}{1}+\frac{\dot{Q}_1}{1+F_1/\lambda_{SF_6}}+\frac{(1-\dot{Q}_o-\dot{Q}_1)}{1+F_2/\lambda_{SF_6}} = R_{SF_6} \quad (26)$$

(d) These "trial R" are compared with the R published by Wagner and colleagues (1978), and

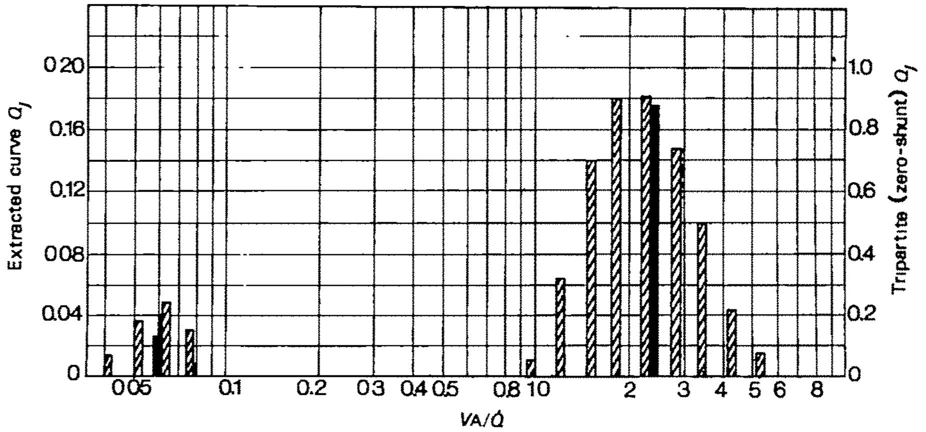

FIG. 7. Published curve (Wagner et al., 1978) for patient No. 3 with ordinate converted to fractional perfusion per compartment (cross-hatched bars). Solid bars represent the "tripartite" distribution (in this case the shunt compartment $\dot{Q}_o = 0$) derived from the extracted R.

TABLE VI. *Summary of analysis of published values of* R *and* λ *and graphical distributions (fig. 1) for first four patients (Wagner et al., 1978). These* R *and* λ *values for patient 1 are accurately matched by a bipartite distribution.* R *and* λ *for patient 2 are coarsely matched by a tripartite distribution with* $\dot{Q}_0 = 0$. R *and* λ *for patients 3 and 4 cannot be matched by* ANY *distributions because their log* R *v. log* λ *plotted points do not fall on a smooth monotonic curve. Sample distributions (out of the infinitude of just-as-bad distributions yielding* R *with similar large errors) are provided. However, when the published distribution curves for these patients are extracted, the extracted* R *are closely matched by tripartite distributions. Eth. = Ethane; Cyclo. = cyclopropane; Hal. = halothane*

Patient No.	Compartmental specifiers					Percent difference in retentions					
	$\dot{Q}_0$	$\dot{Q}_1$	$\dot{Q}_2$	F_1	F_2	SF_6	Eth.	Cyclo	Hal.	Ether	Acetone
1											
Published *R*	0.0408	0.9592	—	0.660	—	+0.57	−2.8	+1.4	+0.84	+0.11	+0.0004
Extracted *R*	0.0404	0.9596	—	0.535	—	−0.0057	−1.6	+0.54	+0.89	+0.29	0
2											
Published *R*	0	0.473	0.527	0.367	2.108	+3.5	−3.7	+3.4	+2.9	+0.16	−0.024
3											
Published *R*	0.0007	0.097	0.9028	0.22	2.38	+9.2	−24.2	+5.0	+6.0	+1.0	+0.02
Extracted *R*	0	0.13	0.87	0.061	2.20	−0.001	+0.45	−1.23	+0.002	+0.38	—
4 (control)											
Published *R*	0	0.134	0.866	0.131	0.767	+0.023	−22.2	−0.12	+0.83	+0.50	+0.02
Extracted *R*	0	0.236	0.764	0.105	0.94	+0.01	−0.106	+0.014	−0.019	+0.13	—

the procedures described under '*The "inverse" operation*', above, are carried out. (We have found that, in simulations, the sum of the absolute errors is always less than about 2.0%.) This method is illustrated by figures 6 and 7. Note that the bipartite compartments matching the published *R* are displaced from the distribution curve obtained by Wagner and colleagues (1978) (fig. 6), while the bipartite compartments matching the *extracted R* very neatly fit the curve from which they were extracted. Table VI summarizes the results of applying this method to patients Nos 1–4 studied by Wagner and colleagues.

It is found that the published values of *R* for patients 3 and 4 cannot be matched by a tripartite distribution. When the logs of the published *R* are plotted *v.* the logs of the values of λ, all of the points do not fall on a smooth monotonic curve. This is evidence either that published sets of (*R*, λ) contain substantial errors in determination of (*R*, λ, or that the multiple inert gas method model is inadequate. However, when the published distribution graphs are extracted (the published λ accepted), the resulting extracted *R* are shown to be exactly matched by tripartite or bipartite solutions. It is evident that the multiple inert gas method provided distribution curves which are misleading in two ways. First, the *R* of those curves (extracted *R*) are not the same as the measured (published) *R*. Second, many very differently shaped curves can yield sets of *R* identical to the extracted *R* of those curves (fig. 8), and no logical reason for choosing the particular shapes published has been provided by Wagner and colleagues in the literature to date.

Inherent restrictions on resolution

In order to investigate the range limits of continuous distributions "matchable" by tripartite distributions, the following continuous distributions were studied (fig. 8). (a) A one-hump-no-shunt lognormal curve ($\sigma = 1$ log unit; $\pm\sigma$ denotes a range of $\dot{V}_A/\dot{Q}$ of 100–1) extending over the $\dot{V}_A/\dot{Q}$ range 0.005–100. (b) A two-hump lognormal curve with shunt yielding sets of *R* matching (a). (c) A three-hump lognormal curve with shunt also yielding matching sets of *R*. (d) The tripartite distribution matching (a), (b) and (c). Note the widely varying $\dot{V}_A/\dot{Q}$ distribution shapes with indistinguishable retentions. (The values for λ used in all these calculations are: SF_6 0.008; enflurane 0.09; cyclopropane 0.55; halothane 2.7; ether 12; and acetone 200.) Table

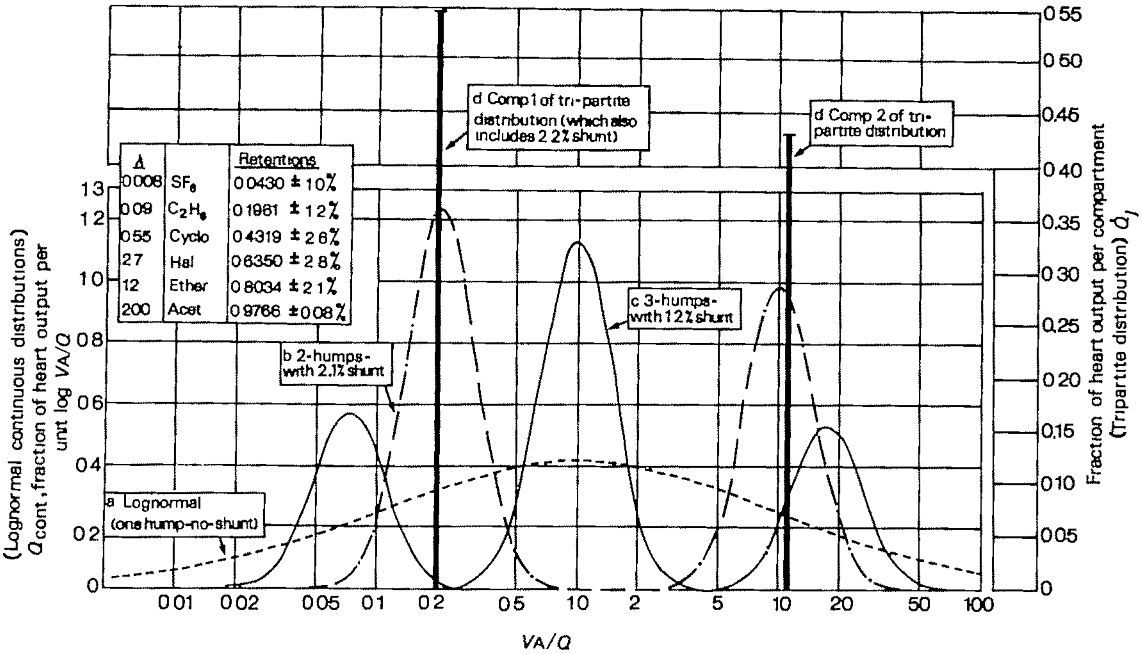

FIG. 8. Four distributions selected from the infinitude of distributions yielding sets of retentions indistinguishable from one another.

TABLE VII. *Four "matching" distributions; three lognormal distributions and the unique "tripartite" (two-compartment-plus-shunt) distribution. †Compartments, not humps. Eth. = Ethane; Cyclo. = cyclopropane; Hal. = halothane; Acet. = acetone*

Distribution No.	No. humps	Shunt (%)	Centre of hump (or compartment) No. 1 $(\dot{V}A/\dot{Q})_1$	No. 2 $(\dot{V}A/\dot{Q})_2$	No. 3 $(\dot{V}A/\dot{Q})_3$	σ of hump(s) ($\log_{10}$ units)	Proportion of perfusion in Hump No. 1 ($\dot{Q}_1$)	Hump (No. 2 $\dot{Q}_2$)	Hump No. 3 ($\dot{Q}_3$)
1	1	0		1.0		1	100%		
2	2	2.13	0.2080	10		0.176	54.6%	43.3%	
3	3	1.22	0.0735	1.0	17.378	0.176	25.4%	50%	23.4%
4	2†	2.20	0.2033	10.853	none	n/a	54.8%†	43.0%†	

Distribution No.	No. humps	Shunt (%)	% Errors from mean retentions SF₆	Eth.	Cyclo.	Hal.	Ether	Acet.
1	1	0	−0.97	+1.23	−2.56	+1.65	+2.1	−0.08
2	2	2.13	+0.98	−1.14	+1.70	−2.26	−1.38	+0.08
3	3	1.22	−0.04	+0.19	−2.36	+2.84	+2.02	+0.07
4	2†	2.20	+0.11	+1.23	+2.56	−2.84	−2.10	+0.08
"Mean" retentions of all distributions			0.04300	0.196135	0.431928	0.634995	0.803443	0.976565

VII summarizes the compartmental details and shows the percent errors of exact match of the tripartite and these continuous distributions. Note the *maximum* error of ±2.84% (RMS error 1.67%) even though these distributions extend unnaturally widely.

Additionally, we studied various "flat" continuous distributions. In a flat distribution the cardiac output is distributed equally over a designated continuous substantial range of $\dot{V}A/\dot{Q}$. The perfusion ordinate, which previously has been "fraction of cardiac output per compart-

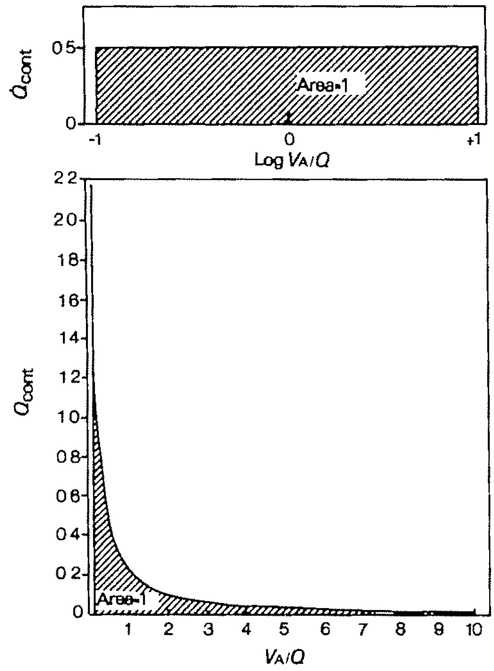

FIG. 9. A continuous distribution, flat in log($\dot{V}_A/\dot{Q}$) (above), and the same distribution plotted with linear $\dot{V}_A/\dot{Q}$ (below).

ment", becomes "fraction of cardiac output per unit abscissa", so that a distribution flat in log $\dot{V}_A/\dot{Q}$ is vastly different from the flat distribution in a graph where $\dot{V}_A/\dot{Q}$ (not log $\dot{V}_A/\dot{Q}$) is the abscissa (fig. 9). Nevertheless, both types of flat distributions are well matched by tripartite distributions (table VIII). Note that No. 3, flat in log $\dot{V}_A/\dot{Q}$ over a range of 10000:1, is matched by a tripartite distribution with a maximum error of ±3.13% (RMS error = 2.0%)!

Resolution unaffected by additional tracer gases

We studied the accuracy of match of a tripartite distribution to its continuous flat distribution counterpart. If increased resolution were to result from using more tracer gases, the match by a tripartite distribution would disappear. However, as shown by figure 10, the percent difference between a flat, continuous (log) distribution over a 100:1 range of $\dot{V}_A/\dot{Q}$ oscillates about zero (max. ±2.2%), and approaches zero above $\lambda = 200$. Thus no increased resolution is attainable by the use of more tracer gases.

ACTUAL ACHIEVEMENT OF MULTIPLE INERT GAS METHOD

In contrast to the era before the multiple inert gas method was available, whereby shunt and *one* alveolar compartment could be resolved, the multiple inert gas method allows the calculation of shunt and *two* alveolar compartments. This is illustrated by figure 11. It would seem that, if one were to choose a specific distribution (out of the infinitude of possibilities resulting in the same set of retentions) as representative for ease of description and communication, the two-alveolar-compartment-plus-shunt model (sometimes one or two compartments may be unoccupied), which is also unique, being the simplest form, unadorned by speculative decoration, would be the logical choice. Of course, a caveat should accompany

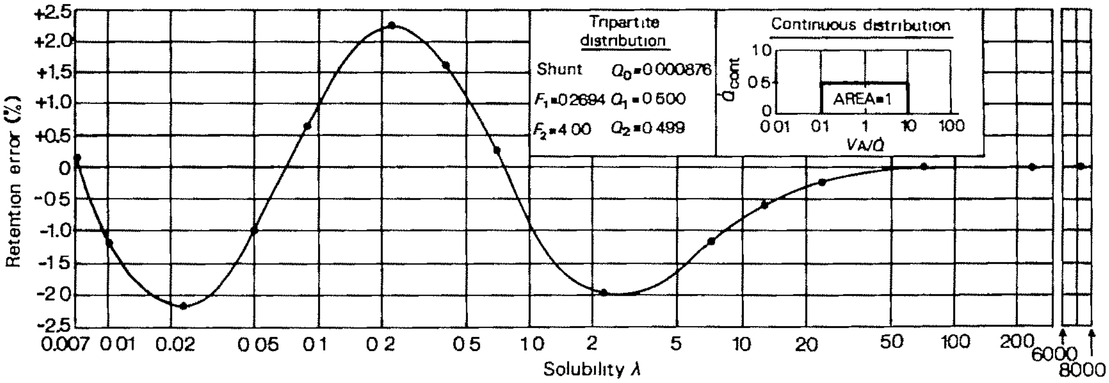

FIG. 10. Percent difference in retentions calculated from the indicated tripartite distribution compared with the retentions calculated from the indicated "flat" (in log F) distribution for 16 tracers ranging from $\lambda = 0.007$ to $\lambda = 7000$. The ordinate in the "continuous distribution" graph is fractional perfusion per unit log($\dot{V}_A/\dot{Q}$).

TABLE VIII. *Sample flat distributions*: $\dot{V}_A/\dot{Q}$ *log or linear, range limits, retentions as determined by calculus; the perfusions and* $\dot{V}_A/\dot{Q}$ *values of the "matching" tripartite and bipartite distributions; and the percent deviation (error) of their retentions from a set of mean retentions. Eth. = Ethane; Cyclo. = cyclopropane; Hal. = halothane; Acet. = acetone*

No.	$\dot{V}_A/\dot{Q}$ or $\log \dot{V}_A/\dot{Q}$	Range limits	R of flat distribution					
			SF_6	Eth.	Cyclo.	Hal.	Ether	Acet.
1	log	0.10–10	0.0165	0.1374	0.3948	0.6717	0.8702	0.9895
2	log	0.01–10	0.0850	0.3320	0.5749	0.7763	0.9124	0.9929
3	log	0.01–100	0.0638	0.2499	0.4365	0.6053	0.7576	0.95598
4	$\dot{V}_A/\dot{Q}$	0.10–10	0.00366	0.0361	0.1548	0.41236	0.7247	0.9756
5	$\dot{V}_A/\dot{Q}$	0.01–10	0.00506	0.04157	0.16164	0.41747	0.7271	0.9758
6	$\dot{V}_A/\dot{Q}$	0.01–100	0.00069	0.00622	0.02855	0.09815	0.268	0.8109
7	log	0.45–1.42	0.0104	0.1051	0.4098	0.7662	0.9346	0.9958
8	log	0.253–2.53	0.0122	0.1170	0.4162	0.7518	0.9260	0.9951
9	$\dot{V}_A/\dot{Q}$	0.45–1.42	0.0094	0.0953	0.3842	0.7470	0.9281	0.9953
10	$\dot{V}_A/\dot{Q}$	0.253–2.53	0.0080	0.0804	0.3247	0.6778	0.8983	0.9931

No.	$\dot{V}_A/\dot{Q}$ or $\log \dot{V}_A/\dot{Q}$	Range limits	Two-compartment-plus-shunt distribution				
			$\dot{Q}_0$	$\dot{Q}_1$	$\dot{Q}_2$	$(\dot{V}_A/\dot{Q})_1$	$(\dot{V}_A/\dot{Q})_2$
1	log	0.10–10	0.00914	0.4821	0.517	0.2568	3.8555
2	log	0.01–10	0.0375	0.564	0.3985	0.089	3.320
3	log	0.01–100	0.0347	0.5214	0.4439	0.1359	20.99
4	$\dot{V}_A/\dot{Q}$	0.10–10	0.000146	0.1774	0.8225	0.586	5.885
5	$\dot{V}_A/\dot{Q}$	0.01–10	0.000449	0.0898	0.9098	0.2188	4.97
6	$\dot{V}_A/\dot{Q}$	0 01–100	0.000171	0.0952	0.9046	1.981	52.55
			One-compartment-plus-shunt distribution				
7	log	0.45–1.42	0.00031	0.99969		0.7797	
8	log	0.253–2.53	0.00134	0.99866		0.7277	
9	$\dot{V}_A/\dot{Q}$	0.45–1.42	0.00025	0.99975		0.86856	
10	$\dot{V}_A/\dot{Q}$	0.253–2.53	0.00080	0.9992		1.098	

No.	$\dot{V}_A/\dot{Q}$ or $\log \dot{V}_A/\dot{Q}$	Range limits	Error (%)					
			SF_6	Eth.	Cyclo.	Hal.	Ether	Acet.
1	log	0.10–10	0.066	0.281	−0.184	−2.62	−0.689	0.0091
2	log	0.01–10	0.031	−0.135	0.805	−1.82	−0.316	0.030
3	log	0.01–100	0.144	−2.21	6.35	−3.9	−6.04	0.158
4	$\dot{V}_A/\dot{Q}$	0.10–10	−0.221	0.102	0.961	−1.89	−0.489	0.042
5	$\dot{V}_A/\dot{Q}$	0.01–10	0.336	2.97	−3.89	−3.27	0.677	0.212
6	$\dot{V}_A/\dot{Q}$	0.01–100	0.541	−5.63	6.14	1.50	−6.28	0.132
7	log	0.45–1.42	0.254	−1.29	0.975	1.272	0.465	0.032
8	log	0.253–2.53	0.38	−4.91	3.62	4.82	1.83	0.13
9	$\dot{V}_A/\dot{Q}$	0.45–1.42	0.07	−1.26	0.959	1.30	0.48	0.034
10	$\dot{V}_A/\dot{Q}$	0.253–2.53	0.43	−4.82	2.93	4.92	2.0	0.145

TABLE VIII. (*cont.*)

No.	$\dot{V}_A/\dot{Q}$ or $\log \dot{V}_A/\dot{Q}$	Range limits	Error from a set of mean retentions (%)					
			Flat distribution					
			SF_6	Eth.	Cyclo.	Hal.	Ether	Acet.
1	log	0.10–10	−0.033	−0.141	+0.092	+1.31	+0.345	−0.005
2	log	0.01–10	−0.015	0.067	−0.402	0.91	0.158	−0.015
3	log	0.01–100	−0.072	1.10	−3.13	+1.95	+3.0	−0.079
4	$\dot{V}_A/\dot{Q}$	0.10–10	0.11	−0.05	−0.48	+0.94	+0.25	−0.021
5	$\dot{V}_A/\dot{Q}$	0.01–10	−0.17	−1.48	+1.94	1.63	−0.34	−0.11
6	$\dot{V}_A/\dot{Q}$	0.01–100	−0.27	2.81	−3.1	−0.75	3.1	−0.07
7	log	0.45–1.42	−0.13	+0.65	−0.49	−0.64	−0.23	−0.02
8	log	0.253–2.53	−0.19	2.45	−1.80	−2.40	−0.91	−0.07
9	$\dot{V}_A/\dot{Q}$	0.45–1.42	−0.04	0.63	−0.48	−0.65	−0.24	−0.02
10	$\dot{V}_A/\dot{Q}$	0.253–2.53	−0.22	+2.41	−1.5	−2.45	−1.0	−0.07

No.	$\dot{V}_A/\dot{Q}$ or $\log \dot{V}_A/\dot{Q}$	Range limits	Error from a set of mean retentions (%)					
			Two-compartment-plus-shunt distribution					
			SF_6	Eth.	Cyclo.	Hal.	Ether	Acet.
1	log	0.10–10	0.033	0.141	−0.092	−1.31	−0.345	0.005
2	log	0.01–10	0.015	−0.067	0.402	−0.91	−0.158	0.015
3	log	0.01–100	0.072	−1.10	3.13	−1.95	−3.0	0.079
4	$\dot{V}_A/\dot{Q}$	0.10–10	−0.11	0.05	0.48	−0.94	−0.25	0.021
5	$\dot{V}_A/\dot{Q}$	0.01–10	0.17	1.48	−1.94	−1.63	0.34	0.11
6	$\dot{V}_A/\dot{Q}$	0.01–100	0.27	−2.81	3.1	0.75	−3.1	0.07
			One-compartment-plus-shunt distribution					
7	log	0.45–1.42	0.13	−0.65	0.49	0.64	0.23	0.02
8	log	0.253–2.53	0.19	−2.45	1.80	2.40	0 91	0.07
9	$\dot{V}_A/\dot{Q}$	0.45–1.42	0.04	−0.63	0.48	0.65	0.24	0.02
10	$\dot{V}_A/\dot{Q}$	0.253–2.53	0.22	−2.41	1.5	2.45	1.0	0.07

each such model, warning that the true distribution is certainly not that one.

RELATIONSHIP BETWEEN BLOOD-GAS TENSIONS (Pa_{O_2} AND Pa_{CO_2}) AND $\dot{V}_A/\dot{Q}$ DISTRIBUTION

Arterial blood-gas tensions depend upon the $\dot{V}_A/\dot{Q}$ distribution in much the same way that retentions depend upon $\dot{V}_A/\dot{Q}$ distributions. The non-linearity of the "solubility" of oxygen and of carbon dioxide seemingly complicates the mathematics, so that the proponents of the multiple inert gas method considered "inert gases the tracers of choice" (Olszowka and Wagner, 1980) in the determination of the $\dot{V}_A/\dot{Q}$ distribution. In the light of our determination of the limited resolution attained by the method, three questions about the interaction of the $\dot{V}_A/\dot{Q}$ distribution and "blood gases" arose. First, could more resolution in the $\dot{V}_A/\dot{Q}$ distribution be achieved if blood-gas measurements were made in addition to inert gas retentions? Second, can the unique tripartite (or bipartite) $\dot{V}_A/\dot{Q}$ distribution be determined from blood-gas measurements as accurately as from retention determination? Third, can more information about the distribution be gleaned from a "blood-gas" system than from the multiple inert gas method?

To answer these questions, one of us (R.D.K.) developed a comprehensive Fortran program which calculates the blood-gas tensions when a $\dot{V}_A/\dot{Q}$ distribution and all other haemodynamic, metabolic and ventilatory values are specified.

This program, and the considerations, assumptions, theories upon which it is based and validation, are presented in the companion paper

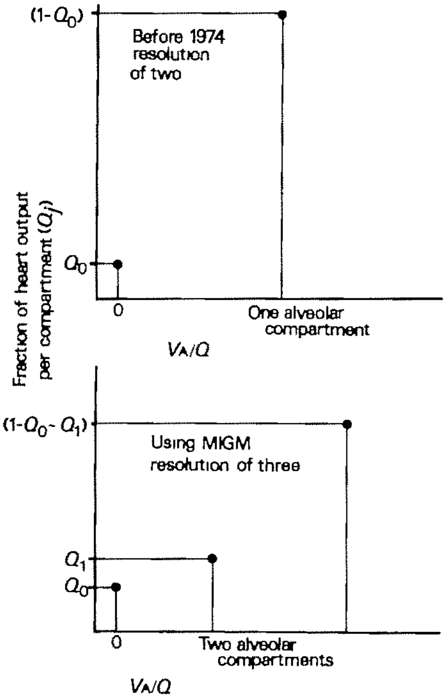
(1-Q_0)
Before 1974 resolution of two
Fraction of heart output per compartment (Q_j)
Q_0
0
One alveolar compartment
VA/Q
(1-Q_0-Q_1)
Using MIGM resolution of three
Q_1
Q_0
0
Two alveolar compartments
VA/Q

FIG. 11. Increase in "resolution" (pertaining to *perfused* compartments) attained by multiple inert gas methodology (MIGM).

(Kaufman, Patterson and Lee, 1987) along with results of computer experiments illustrating in detail the expected accuracy of the $\dot{V}A/\dot{Q}$ distribution determination using oxygen and carbon dioxide as "tracers."

It seemed logical to compare the "resolving power" of the multiple inert gas method with that of a "blood-gas" system—that is, one based upon measurements of oxygen and carbon dioxide. As an initial test we compared the minimal detectable broadening of an initially extremely narrow lognormal distribution (actually a single compartment; the dispersion, σ, being zero) using the two methods.

A graph (fig. 12) was constructed with σ on the abscissa, and an indication of the R "error", or change in R, which ensues as the distribution is broadened over the σ range 0–0.25 log units. This indication is based upon that retention which showed the greatest percentage change, or error, regardless of sign. Then, assuming that 5 % is the minimal detectable difference, or analytical error, in R achievable by the multiple inert gas method, the absolute value of that greatest percentage error is divided by 5, so that the units are

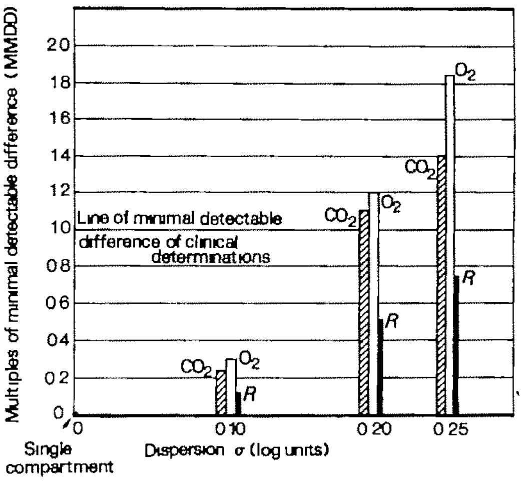

FIG. 12. The inert gas retention, Pa_{O_2} and Pa_{CO_2} consequences of broadening a lognormal "compartment" (centred at $\dot{V}A/\dot{Q} = 0.8$), starting with a single (maximally sharp, $\sigma = 0$) compartment. The ordinate is in multiples of minimal detectable difference between each lognormal distribution and its best matching bipartite distribution ("error"), so that unity represents the least difference which may be measured. Thus errors in retention (R), Pa_{O_2} (O_2) and Pa_{CO_2} (CO_2) may be directly compared. Calculations used the following values: $pH\bar{v} = 7.36$ initially; initial $P\bar{v}_{CO_2} = 46$ mm Hg (6.1 kPa); $P\bar{v}_{O_2} = 42.5$ mm Hg (5.7 kPa), $PI_{O_2} = 150$ mm Hg (20 kPa); Hct = 45 %, Hb = 15 g dl^{-1}; temperature = 37 °C, $(Ca_{O_2} - C\bar{v}_{O_2}) = 5.0$ mm Hg (0.67 kPa); RQ = 0.8.

"multiples of minimal detectable difference". The greatest error always proved to be in the mid-range-λ gases. We name these indication units "MDD units".

Starting with each chosen log normal distribution without shunt, a set of retentions was calculated. Then a bipartite (one alveolar compartment plus shunt; the amount of shunt is very small) distribution with minimum percentage error (change from the lognormal) was found. We considered the inclusion of a small amount of shunt to be proper, because there is no way to determine in a real lung whether or not that amount of shunt exists.

Figure 12 shows that, at σ = 0.25 log units, the R error is 0.72 MDD units; that is, less than the minimal detectable error. In a lognormal distribution with σ = 0.25 log units, centred at $\dot{V}A/\dot{Q} = 0.8$, 68 % of the perfusion exists between $\dot{V}A/\dot{Q} = 0.45$ and 1.42. This broadly dispersed distribution cannot be distinguished from that of a single compartment centred at $\dot{V}A/\dot{Q} = 0.744$ with 0.09 % shunt.

In a similar way the relationship between σ and the "error" or change in blood-gas tensions in the best matching bipartite distribution was graphed. Again the error is expressed in MDD units, assuming that Pa_{O_2} determinations are accurate within 5 %, and Pa_{CO_2} within 2 mm Hg (0.27 kPa). The blood-gas values resulting from each distribution were calculated by Kaufman's Program at PI_{O_2} of 110 mm Hg (14.8 kPa), 150 mm Hg (20 kPa) and 350 mm Hg (46.6 kPa), at nominal values of other measurable variables: $pH_{\bar{v}} = 7.36$; $P\bar{v}_{CO_2} = 46$ mm Hg (6.1 kPa); $P\bar{v}_{O_2} = 42.5$ mm Hg (5.7 kPa); Hct = 45 %; Hb = 15 g dl^{-1}; temperature = 37 °C; $(Ca_{O_2} - C\bar{v}_{O_2}) = 5$ mm Hg (0.67 kPa); RQ = 0.80. The criteria of "best match" of a bipartite to its lognormal distribution were chosen to be as follows. First, the Pa_{CO_2} error at $PI_{O_2} = 150$ mm Hg (20 kPa) must be equal to that at 350 mmHg (46.6 kPa). Second, the Pa_{O_2} error at 150 mm Hg (20 kPa) must be the negative of the error at 350 mm Hg (46.6 kPa). Finally, the errors expressed in MDD units must be in the same range for both oxygen and carbon dioxide. The blood-gas error data are plotted on the same graph as the multiple inert gas method R error data.

In figure 12 the $\sigma = 0.25$ log unit–lognormal distribution is seen to be best matched by a single compartment at $\dot{V}\text{A}/\dot{Q} = 0.84$ with a 2.45 % shunt. This bipartite distribution produces a Pa_{O_2} error of 1.8 MDD units, while the Pa_{CO_2} error is 1.4 MDD units. Thus, a 0.25-σ lognormal distribution cannot be matched by any single compartment plus shunt in the blood-gas method, and it follows that the resolution of the blood-gas method appears to be at least as detailed as the multiple inert gas method with respect to this particular aspect (or test) of resolution.

APPENDIX A

ABBREVIATIONS

α	Rate of injection of tracer gas (ml (STPD) min^{-1}).
C	Concentration (content) (ml (STPD) $litre^{-1}$).
Ca	Arterial concentration.
Ca_i	Arterial concentration of the gas designated i.
C_{ij}	Concentration of the ith tracer gas leaving the jth compartment.
C_{in}	Concentration in blood entering the model lung (fig. 1).
C_j	Concentration of tracer gas in blood leaving the compartment designated j.
C_{out}	Concentration in blood leaving the model lung (fig. 1).
$C\bar{v}$	Concentration in mixed venous blood (ml (STPD) $litre^{-1}$).
$C\bar{v}_i$	Mixed venous concentration of the ith tracer gas.
F	Ventilation–perfusion ratio = $\dot{V}\text{A}/\dot{Q}$ $\left(\frac{\text{litre min}^{-1}\text{ of air}}{\text{litre min}^{-1}\text{ of blood}}\right)$
F_j	$\dot{V}\text{A}/\dot{Q}$ for the jth compartment.
λ	Blood:gas partition coefficient.
λ_i	Partition coefficient of the gas designated i.
n	Blood volume (litre).
$\dot{n}$	Blood flow (litre min^{-1}).
$\dot{Q}$	Cardiac output (litre of blood min^{-1}).
$\dot{Q}_{cont}$	Fraction of total heart output per unit abscissa. (Used where distribution is continuous, not compartments.)
$\dot{Q}_j$	Fraction of the total heart output going to the jth compartment.
R	Retention, the ratio of arterial to mixed venous partial pressures (concentrations) of a tracer inert gas.
$\sum\limits_{j=a}^{j=b}$	Summation of all terms with j (a whole number) having values from a to b.
STPD	Standard temperature and pressure, dry.
$\dot{V}\text{A}$	Total alveolar ventilation (litre min^{-1}).
$\dot{V}\text{A}/\dot{Q}$	Ratio of ventilation to perfusion.
$\dot{V}\text{D}$	Deadspace minute volume (litre min^{-1}).
$\dot{V}\text{E}$	Exhalation minute volume (litre min^{-1}).
$\dot{V}_j$	Ventilation of the jth compartment (litre min^{-1}).

APPENDIX B

CALCULATED EXAMPLE

Substituting $(1-\dot{Q}_1)$ for $\dot{Q}_o$ in equation (20):

$$1-\dot{Q}_1+\dot{Q}_1/(1+F_1/0.092) = 0.38947$$

$$1-\dot{Q}_1+0.092\,\dot{Q}_1/(F_1+0.092) = 0.38947$$

$$\frac{F_1+0.092-F_1\dot{Q}_1-0.092\,\dot{Q}_1+0.092\,Q_1}{F_1+0.092} = 0.38947$$

$$F_1+0.092-F_1\dot{Q}_1 = 0.38947\,F_1+0.03583$$

$$\dot{Q}_1 = \frac{F_1(0.38947-1)+0.03583-0.092}{-F_1}$$

$$\dot{Q}_1 = \frac{0.61053\,F_1+0.05617}{F_1}$$

Substituting $(1-\dot{Q}_1)$ for $\dot{Q}_o$ in equation (21):

$$1-\dot{Q}_1+\dot{Q}_1/(1+F_1/2.3) = 0.7981 \tag{27}$$

$$1-\dot{Q}_1+2.3\,\dot{Q}_1/(F_1+2.3) = 0.7981$$

$$\frac{F_1+2.3-F_1\dot{Q}_1-2.3\,\dot{Q}_1+2.3\,\dot{Q}_1}{F_1+2.3} = 0.7981$$

$$F_1+2.3-F_1\dot{Q}_1 = 0.7981\,F_1+1.83563$$

$$\dot{Q}_1 = \frac{F_1(0.7981-1)+1.83563-2.3}{-F_1}$$

$$\dot{Q}_1 = \frac{0.2019\,F_1+0.4644}{F_1}$$

Therefore:

$$0.61053\,F_1+0.05617 = 0.2019\,F_1+0.4644$$

$$0.4086\,F_1 = 0.4082$$

$$F_1 = 0.999$$

Substituting for F_1 in equation (27):

$$1-\dot{Q}_1+\dot{Q}_1/(1+0.999/2.3) = 0.7981$$

$$-\dot{Q}_1+\dot{Q}_1/1.4343 = -0.2019$$

$$-1.4343\,\dot{Q}_1+\dot{Q}_1 = -0.28959$$

$$-0.4343\,\dot{Q}_1 = -0.28959$$

$$\dot{Q}_1 = 0.6667$$

Finally, substituting for $\dot{Q}_1$ in equation (19):

$$\dot{Q}_o+0.6667 = 1$$

$$\dot{Q}_o = 0.3333$$

APPENDIX C

SOLUTION OF EQUATIONS

$\dot{Q}_2 = 1-\dot{Q}_1$ may be substituted into equation (18), producing:

$$\dot{Q}_1/(F_1+\lambda)+1/(F_2+\lambda)-\dot{Q}_1/(F_2+\lambda) = R/\lambda \qquad (28)$$

Multiplying each term by $(F_1+\lambda)(F_2+\lambda)$:

$$\dot{Q}_1(F_2+\lambda)+(F_1+\lambda)-\dot{Q}_1(F_1+\lambda) = R(F_1+\lambda)(F_2+\lambda)/\lambda$$

$$\dot{Q}_1(F_2+\lambda-F_1-\lambda) = R(F_1+\lambda)(F_2+\lambda)/\lambda-(F_1+\lambda)$$

$$\dot{Q}_1 = \frac{(F_1+\lambda)(F_2R/\lambda+R-1)}{F_2-F_1} \qquad (29)$$

This equation may be written for each tracer gas, and since (F_2-F_1) is the same for both ethane (e) and halothane (h):

$$(F_1+\lambda\mathrm{e})(F_2R\mathrm{e}/\lambda\mathrm{e}+R\mathrm{e}-1) = (F_1+\lambda\mathrm{h})(F_2R\mathrm{h}/\lambda\mathrm{h}+R\mathrm{h}-1)$$

$$F_1(F_2R\mathrm{e}/\lambda\mathrm{e}-F_2R\mathrm{h}/\lambda\mathrm{h}+R\mathrm{e}-R\mathrm{h}) = F_2R\mathrm{h}-F_2R\mathrm{e} + \lambda\mathrm{h}R\mathrm{h}-\lambda\mathrm{e}R\mathrm{e}+\lambda\mathrm{e}-\lambda\mathrm{h}$$

$$F_1 = \frac{F_2R\mathrm{h}-F_2R\mathrm{e}+\lambda\mathrm{h}R\mathrm{h}-\lambda\mathrm{e}R\mathrm{e}+\lambda\mathrm{e}-\lambda\mathrm{h}}{F_2R\mathrm{e}/\lambda\mathrm{e}-F_2R\mathrm{h}/\lambda\mathrm{h}+R\mathrm{e}-R\mathrm{h}} \qquad (30)$$

This equation, together with equations (28) and (24), permits quick calculation of the desired values.

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DERIVATION OF $\dot{V}\mathrm{A}/\dot{Q}$ DISTRIBUTION FROM BLOOD-GAS TENSIONS

R. D. KAUFMAN, R. W. PATTERSON AND A. ST J. LEE

SUMMARY

Gas exchange was modelled by a Fortran program. Arterial blood-gas tensions have higher resolution than inert gas retentions in terms of distinguishing a single $\dot{V}\mathrm{A}/\dot{Q}$ compartment from a progressively broadening lognormal distribution. The maximum number of compartments determinable by arterial blood-gas tensions is three; $\dot{V}\mathrm{A}/\dot{Q}$ distributions containing more compartments are non-unique. Without utilizing 100% inspired oxygen, arterial blood-gas tensions cannot resolve the relative perfusion in shunt and low-$\dot{V}\mathrm{A}/\dot{Q}$ compartments, but the total perfusion in these compartments is determinable. The way in which the arterial blood-gas tensions vary with the variables of two and three-compartment distributions is described. Two- and three-compartment $\dot{V}\mathrm{A}/\dot{Q}$ distributions are derivable from either arterial blood-gas tensions or inert gas retentions.

The companion paper (Lee, Patterson and Kaufman, 1987) derives the retention equations upon which the Multiple Inert Gas Method is based. It is shown that the resolution is limited: namely, three perfused compartments at most. In this paper we examine whether the use of blood-gas tensions can give the same or more information. Blood-gas tensions have the advantages that they are incomparably easier to measure, the measurements are more accurate in many instances, and the equipment is almost universally available.

The following questions were investigated: (1) What is the relative resolution of the blood-gas method compared with the multiple inert gas method? (2) Can markedly different distributions result in the same arterial blood-gas tensions? (3) Can arterial blood-gas tensions resolve shunt from low $\dot{V}\mathrm{A}/\dot{Q}$ compartments? (4) Knowing the arterial blood-gas tensions, what are the mechanics of fitting a tripartite distribution? (5) Can the blood-gas method produce the same results as the multiple inert gas method?

(Abbreviations used throughout this paper are listed in Appendix A.)

COMPUTER MODEL

Gas exchange was modelled by a Fortran program written by one of the authors (R.D.K.). The lung was modelled with up to 42 individual perfused compartments, shunt and 41 ventilated compartments. Deadspace was not included, since only the ratio of alveolar ventilation to perfusion was relevant in this study. The fraction of cardiac output to each compartment could be explicitly specified, or lognormal distributions containing one, two or three peaks could be specified. In the latter case, the centre, dispersion and fraction of cardiac output to each lognormal peak were specified. The lognormal distributions were comprised of compartments ranging in $\dot{V}\mathrm{A}/\dot{Q}$ from 0.01 to 100. The $\dot{V}\mathrm{A}/\dot{Q}$ spacing of the compartments was linear in log $\dot{V}\mathrm{A}/\dot{Q}$, each compartment separated by 0.1 log unit (26%) (Lee, Patterson and Kaufman, 1987). Compartment No. 1 had log $\dot{V}\mathrm{A}/\dot{Q} = -2.0$, compartment No. 2 had log $\dot{V}\mathrm{A}/\dot{Q} = -1.9$, and compartment No. 41 had log $\dot{V}\mathrm{A}/\dot{Q} = 2.0$.

$P\mathrm{I}_{\mathrm{CO}_2}$ was assumed to equal zero. Tracheal inspired $P\mathrm{O}_2$ was specified. $P\bar{\mathrm{v}}_{\mathrm{O}_2}$, $P\bar{\mathrm{v}}_{\mathrm{CO}_2}$, $\mathrm{pH}_{\bar{v}}$, haematocrit, haemoglobin and body temperature were specified. Thus the acid–base state of the

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ROBERT D. KAUFMAN, M.D.; RICHARD W. PATTERSON, M.D.; Department of Anesthesiology, University of California, Los Angeles, California, 90024, U.S.A. ARNOLD ST JACQUES LEE, P.E., Department of Anesthesiology, University of California, Los Angeles, California, U.S.A., and Surgery Department, Morehouse School of Medicine, Atlanta, Georgia, U.S.A.
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body was defined. The acid–base state of the body may be as well defined by blood-gas tensions from any site. Arterial blood-gas tensions were calculated by one of the following options:

(1) *Without body loop.* The mixed venous blood-gas tensions remained as specified and the arterial blood-gas tensions resulting from the specified distribution and tracheal $P_{I_{O_2}}$ were calculated.

(2) *With body loop.* ($Ca_{O_2} - C\bar{v}_{O_2}$) and RQ were specified. Mixed venous blood-gas tensions were varied such that the arterial blood-gas tensions resulting from the specified distribution and tracheal P_{O_2} also satisfied the carbon dioxide and oxygen transport implied by the specified ($Ca_{O_2} - C\bar{v}_{O_2}$) and RQ. The mixed venous gas tensions were manipulated in such a way that the base excess was not changed from initial conditions.

With either option, the arterial blood-gas variables calculated were: Pa_{O_2}, Pa_{CO_2}, pH$_a$, Sa_{O_2}, Ca_{O_2} (includes dissolved oxygen) and Ca_{CO_2}. The equivalent mixed venous variables were listed also (see figure 1 for a synopsis of the programme).

The calculated arterial blood-gas tensions should more precisely be called pulmonary vein gas tensions, since any shunt was assumed to be in the lung. If cardiac venous blood returning to the left ventricle has about the same composition as mixed venous blood, one could substitute pulmonary shunt directly for cardiac shunt.

The end-capillary blood-gas tensions of each compartment were calculated by simultaneous solution of a continuity equation (conservation of mass) and the equations of oxygen and carbon dioxide content. Both equations are functions of gas pressure. The calculations of oxygen saturation and carbon dioxide blood content were from Kelman (1966, 1967).

Since the equations relating blood-gas partial pressures and contents are not solved for partial pressure as a function of content, an iterative process was required for their solution. In addition, the Bohr and Haldane effects prevent separate solutions for carbon dioxide and oxygen, thus also requiring iterative calculations. Calculation of blood P_{CO_2} in the alveolar capillary or in the pulmonary vein was made to maintain base excess unchanged from the initial value. The buffer line slope ($dHCO_3/dpH$) was derived from Siggaard-Andersen (1974). Thus pulmonary vein P_{CO_2} and pH were calculated so that total carbon dioxide and base excess were appropriate. The program also calculated inert gas retentions, given the $\dot{V}_A/\dot{Q}$ distribution and the gas solubilities.

Model algorithms

Outlines of the blood-gas algorithms are included in Appendix B. The Fortran program is available from the senior author on request; therefore, the outlines use Fortran variables to assist those who desire to read the program. A list of abbreviations follows the outline of the algorithm.

Model validation

The model was validated with the following tests. Mixed venous blood was "ventilated" by

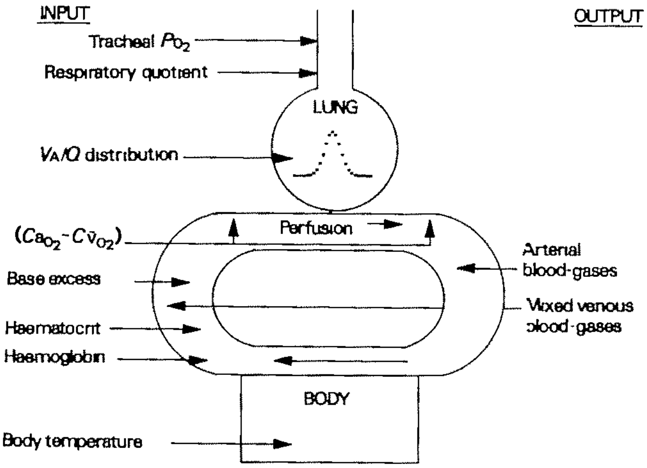


FIG. 1. Diagrammatic synopsis of arterial blood-gas program. Input variables are on the left, calculated output on the right.

the model over a wide range of $\dot{V}\text{A}/\dot{Q}$ values and the constancy of base excess confirmed with the Siggaard-Andersen alignment nomogram. Single compartment "ventilation" of normal mixed venous gases (pH$_{\bar{v}}$ = 7.36; $P\bar{v}_{CO_2}$ = 46 mm Hg (6.1 kPa); $P\bar{v}_{O_2}$ = 42.5 mm Hg (5.7 kPa) with body loop at $\dot{V}\text{A}/\dot{Q} = 0.8$; RQ = 0.85; ($Ca_{O_2} - C\bar{v}_{O_2}$) = 5 ml dl^{-1}; no shunt; on room air (tracheal $P\text{I}_{O_2}$ = 150 mm Hg (20 kPa)) produced arterial blood-gas values of: pH$_a$ = 7.39, Pa_{CO_2} = 40 mm Hg (5.3 kPa), Pa_{O_2} = 104 mm Hg (13.8 kPa). Ventilation under the same circumstances but at $\dot{V}\text{A}/\dot{Q} = 1.6$ or 0.4 produced values of: pH$_a$ = 7.57, Pa_{CO_2} = 20 mm Hg (2.7 kPa), Pa_{O_2} = 128 mm Hg (17.8 kPa); and pH$_a$ = 7.20, Pa_{CO_2} = 81 mm Hg (11.2 kPa), Pa_{O_2} = 56 mm Hg (7.5 kPa), respectively. With the same mixed venous blood and RQ, the arterial blood-gas values were: pH$_a$ = 7.39, Pa_{CO_2} = 40 mm Hg (5.3 kPa), Pa_{O_2} = 104 mm Hg (13.8 kPa) at $\dot{V}\text{A}/\dot{Q} = 1.6$ and ($Ca_{O_2} - C\bar{v}_{O_2}$) = 10 ml dl^{-1}. The arterial blood-gas tensions at different $\dot{V}\text{A}/\dot{Q}$ values with a defined set of mixed venous gases (without body loop) were compared with those predicted by the oxygen-carbon dioxide diagram of Olszowka, Rahn and Farhi (1973) and were found to correspond within 1.5 mm Hg (0.2 kPa) $P\text{CO}_2$ and 4 mm Hg (0.53 kPa) $P\text{O}_2$. The arterial blood-gas tensions with Olszowka's "normal blood chemistry" (($Ca_{O_2} - C\bar{v}_{O_2}$) = 5 ml dl^{-1}, RQ = 0.8, 1% shunt, $\dot{V}\text{A}/\dot{Q}$ distribution with log dispersion = 0.5, tracheal $P\text{O}_2$ = 160 mm Hg (21.3 kPa)) were compared with the maldistribution diagram of Olszowka, Rahn and Farhi (1973) and were found to correspond within 3 mm Hg (0.4 kPa) $P\text{O}_2$.

Error sensitivity of the model

The model requires specification of the variables previously listed. In actual use, these indices would be measured on a patient, entered to the model and the $\dot{V}\text{A}/\dot{Q}$ distribution varied so as to produce the measured arterial blood-gas values. We here examine the effect of measurement error on calculated arterial blood-gas tension.

Haemoglobin and haematocrit. The following combinations were investigated: haemoglobin (Hb) 15 g dl^{-1} with haematocrit (Hct) 40.5%, 45% and 49.5%; Hb 14.5 g dl^{-1} with Hct 39%, 43.5% and 47.9%; Hb 15.5 g dl^{-1} with Hct 42%, 46.5% and 51%. Using these combinations, the arterial blood-gas values resulting from a two-compartment distribution, $\dot{V}\text{A}/\dot{Q} = 0.45$ and $\dot{V}\text{A}/\dot{Q} = 1.4$, equally perfused, were determined with tracheal $P\text{I}_{O_2}$ of 110, 150 and 350 mm Hg (14.6, 20 and 46.6 kPa). The largest error from nominal values (corresponding to Hb 15 g dl^{-1}, Hct 45%) was 0.2 mm Hg (0.027 kPa) in Pa_{CO_2} or Pa_{O_2}. Errors in measurement of Hb or Hct will introduce insignificant errors in arterial blood-gas tension values.

Body temperature. Using the same two-compartment distribution, changing the body temperature from 37 °C to 36 °C or 38 °C resulted in a maximum error of 0.07 mm Hg (0.009 kPa) Pa_{CO_2} and an error of 2.2 mm Hg (0.3 kPa) Pa_{O_2} at 110 mm Hg (14.6 kPa) tracheal $P\text{O}_2$. Error in Pa_{O_2} at 150 or 350 mm Hg (20 or 46.6 kPa) tracheal $P\text{O}_2$ was no greater than 0.4 mm Hg (0.05 kPa). Error in measurement of body temperature will not introduce serious errors.

($Ca_{O_2} - C\bar{v}_{O_2}$). The same two-compartment distribution was utilized with a tracheal $P\text{O}_2$ of 150 mm Hg (20 kPa) to evaluate the effect of errors in measurement of ($Ca_{O_2} - C\bar{v}_{O_2}$). Varying the ($Ca_{O_2} - C\bar{v}_{O_2}$) from a nominal 5 ml dl^{-1} produced an error in Pa_{CO_2} of 1.7 mm Hg (0.23 kPa) and in Pa_{O_2} of 3.8 mm Hg (0.51 kPa) at ($Ca_{O_2} - C\bar{v}_{O_2}$) = 4.75 ml dl^{-1} and 1.8 mm Hg (0.24 kPa) Pa_{CO_2} and 3.7 mm Hg (0.49 kPa) Pa_{O_2} at ($Ca_{O_2} - Cv_{O_2}$) = 5.25 ml dl^{-1}. Thus, a 5% error in ($Ca_{O_2} - C\bar{v}_{O_2}$) resulted in a 4% error in Pa_{O_2} on room air, so that ($Ca_{O_2} - C\bar{v}_{O_2}$) had to be carefully measured to determine the shape and position of the $\dot{V}\text{A}/\dot{Q}$ distribution.

RQ. Using the same distribution and tracheal $P\text{O}_2$, changing the respiratory quotient to 0.75 and 0.85 from a nominal 0.8 resulted in an error in Pa_{CO_2} of 2.2 mm Hg (0.29 kPa) from the nominal value of 34 mm Hg (4.5 kPa). The RQ also had to be carefully measured.

RESULTS

Resolution

We determined the dispersion (σ) at which a progressively broadening lognormal $\dot{V}\text{A}/\dot{Q}$ distribution was measurably different from a two-compartment distribution, one compartment constrained to shunt. One compartment is required to be shunt, since even normal patients have 2–3% shunt. The arterial blood-gas tensions and inert gas retentions were calculated using distributions of σ = 0.1, 0.2 and 0.25 log units centred at $\dot{V}\text{A}/\dot{Q} = 0.794$ (fig. 2). The best matching single compartment with shunt was determined for each of these three distributions,

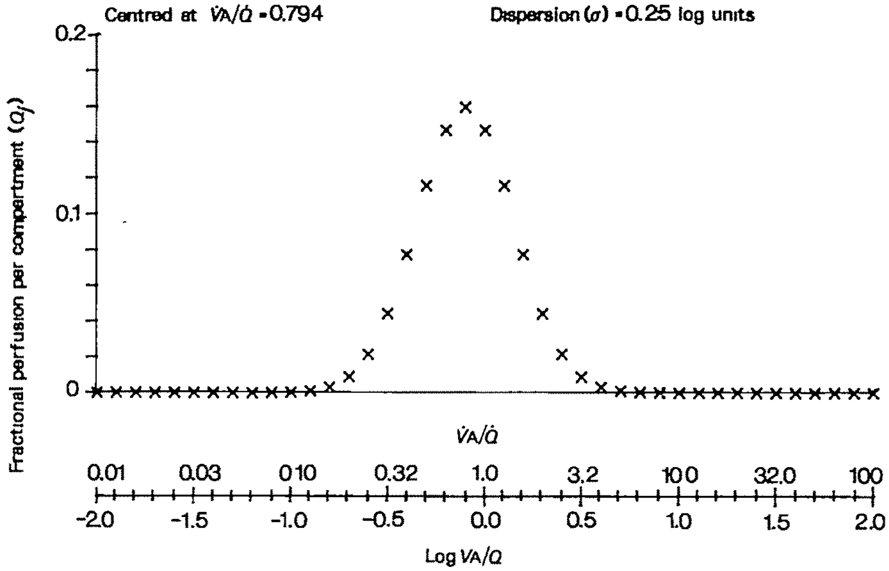


FIG. 2. A single lognormal distribution with the minimum "spread" (σ) which is distinguishable from a single compartment by blood-gas methods. This "spread" is indistinguishable by multiple inert gas methods.

using both retentions and arterial blood-gas tensions as criteria for match. The minimal detectable difference (MDD) in retentions was 5%, assuming an extremely conservative minimal value. The current anaesthetic blood-gas laboratory maximum errors are 5% in Pa_{O_2} and 2 mm Hg (0.27 kPa) in Pa_{CO_2}. Thus we chose these values for the MDD. The retentions from the best matching single compartment with shunt and from the $\sigma = 0.25$ distribution were indistinguishable (0.8 MDD). The arterial blood-gas tensions easily distinguished the best matching single compartment with shunt from the lognormal distribution ($Pa_{CO_2} = 1.4$ MDD, $Pa_{O_2} = 1.8$ MDD) (fig. 3). While a single compartment and shunt is indistinguishable by the multiple inert gas method from this lognormal distribution, it is evident that a single compartment will not suffice in the blood-gas method. We found that compartments at $\dot{V}\text{A}/\dot{Q} = 0.45$ and 1.4 with equal perfusion and no shunt perfectly matched the arterial blood-gas tensions of the $\sigma = 0.25$ distribution at tracheal $P\text{I}_{O_2}$ of 110, 150 and 350 mm Hg (14.6, 30 and 46.6 kPa).

Uniqueness

Figure 8 of Lee, Patterson and Kaufman (1987) (p. 1592 of this issue) shows unimodal, bimodal and trimodal lognormal distributions. The dis-

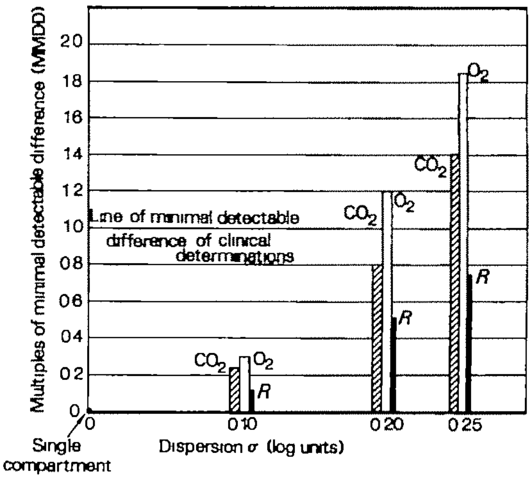


FIG. 3. The inert gas retention, Pa_{O_2} and Pa_{CO_2} consequences of broadening a lognormal distribution (centred at $\dot{V}\text{A}/\dot{Q} = 0.794$), starting with a single (i.e., maximally sharp, $\sigma = 0$) compartment. The ordinate is in multiples of minimal detectable difference between each log normal distribution and its best matching bipartite distribution (i.e. "error"), so that unity represents the least difference which may be measured. Thus, errors in retention (R), Pa_{O_2} (O_2) and Pa_{CO_2} (CO_2) may be directly compared. Calculations used following values: initial $pH_{\bar{v}} = 7.36$, $P\bar{v}_{CO_2} = 46$ mm Hg (6.1 kPa), $P\bar{v}_{O_2} = 42.5$ mm Hg (5.7 kPa), $P\text{I}_{O_2} = 150$ mm Hg (20 kPa), Hct = 45%, Hb = 15 g dl^{-1}, temperature = 37 °C, $(Ca_{O_2} - C\bar{v}_{O_2}) = 5.0$ ml dl^{-1}, RQ = 0.8.

TABLE I. *The range of combinations of shunt and low-$\dot{V}_A/\dot{Q}$ compartment which produce arterial blood-gas tensions indistinguishable from the tripartite distribution: $\dot{Q}_0 = 0.03$, $\dot{V}_A/\dot{Q}]_{LO} = 0.061$, $\dot{Q}_{LO} = 0.1261$, $\dot{V}_A/\dot{Q}]_{HI} = 2.2$, $\dot{Q}_{HI} = 0.8439$ at 150 and 350 mm Hg (20 and 46.6 kPa) tracheal $P_{I_{O_2}}$. (To be read in conjunction with figure 4.)*

						$P_{I_{O_2}}$ 150 mm hg (20 kPa)		$P_{I_{O_2}}$ 350 mm Hg (46.6 kPa)	
	Shunt (%)	$\dot{Q}_{LO}$	$\dot{Q}_{HI}$	$\dot{V}_A/\dot{Q}]_{LO}$	$\dot{V}_A/\dot{Q}]_{HI}$	Pa_{CO_2} (mm Hg)	Pa_{O_2} (mm Hg)	Pa_{CO_2} (mm Hg)	Pa_{O_2} (mm Hg)
1	0	0.136	0.864	0.032	2.2	16.5	67.6	16.5	170.0
2	1	0.13	0.86	0.041	2.2	16.6	67.4	16.6	174.0
3	**3**	**0.1261**	**0.8439**	**0.061**	**2.2**	**16.9**	**65.3**	**17.0**	**176.0**
4	5	0.115	0.835	0.08	2.2	17.1	64.3	17.2	177.0
5	7	0.093	0.837	0.1	2.2	17.1	64.7	17.2	178.0
6	10	0.029	0.873	0.128	2.2	16.3	68.8	16.3	167.0
7	11	0	0.89	—	2.2	—	No Match		—
8	10	0.027	0.873	0.12	2.2	16.3	68.9	16.3	166.0
9	10	0.032	0.868	0.136	2.2	16.4	68.5	16.4	167.0
10	10	0.036	0.864	0.144	2.2	16.5	68.0	16.5	167.0

	(kPa)	(kPa)	(kPa)	(kPa)
1	2.20	8.99	2.20	22.61
2	2.21	8.96	2.21	23.14
3	2.25	8.69	2.26	23.49
4	2.27	8.55	2.29	23.54
5	2.27	8.61	2.29	23.67
6	2.17	9.15	2.17	22.21
7	—	—	—	—
8	2.17	9.16	2.17	22.08
9	2.18	9.12	2.18	22.21
10	2.20	9.04	2.20	22.21

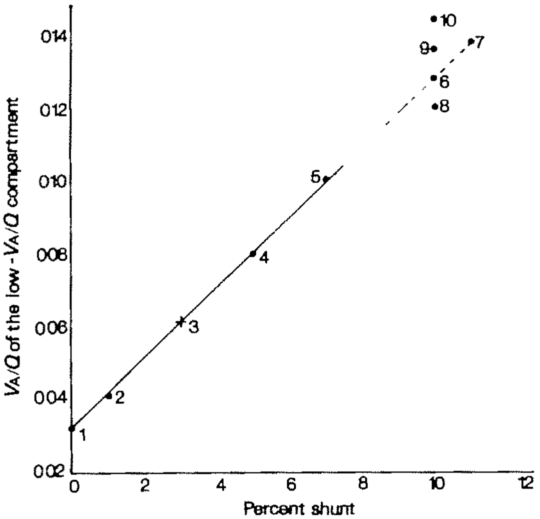


FIG. 4. The range of combinations of shunt and low-$\dot{V}_A/\dot{Q}$ compartment which produce arterial blood-gas values indistinguishable from the tripartite distribution: $\dot{Q}_0 = 0.03$, $\dot{V}_A/\dot{Q}]_{LO} = 0.061$, $\dot{Q}_{LO} = 0.1261$, $\dot{V}_A/\dot{Q}]_{HI} = 2.2$, $\dot{Q}_{HI} = 0.8439$ at 150 and 350 mm Hg (20 and 46.6 kPa) tracheal $P_{I_{O_2}}$. (To be read in conjunction with table I.)

tributions have indistinguishable retentions. The Pa_{CO_2}/Pa_{O_2} values (tracheal $P_{O_2} = 150$ mm Hg (20 kPa)) resulting from the distributions are 11.2/45.8 mm Hg (1.49/6.1 kPa), 9.8/39.1 mm Hg (1.30/5.2 kPa), 11.8/46.4 mm Hg (1.57/6.2 kPa), respectively. This extreme example, probably not compatible with life, demonstrates that complex, multicompartment distributions are not associated with unique arterial blood-gas tensions. As with retentions, only a maximum of three perfused compartments are needed to produce a unique solution.

Shunt v. *low*-$\dot{V}_A/\dot{Q}$

Arterial blood-gas tensions cannot distinguish very low-$\dot{V}_A/\dot{Q}$ compartments from shunt without utilizing 100% inspired oxygen. The values were calculated for patient No. 3 (Wagner et al., 1978; Lee, Patterson and Kaufman, 1987) with 3% shunt added, using the tripartite distribution: shunt = 0.03; $\dot{V}_A/\dot{Q}]_1 = 0.061$, $\dot{Q}_1 = 0.1261$; $\dot{V}_A/\dot{Q}]_2 = 2.2$, $\dot{Q}_2 = 0.8439$. Thus, a total of 15.61% of the perfusion was in shunt plus low-$\dot{V}_A/\dot{Q}$ compartments. Holding $\dot{V}_A/\dot{Q}]_2$ constant, shunt, $\dot{V}_A/\dot{Q}]_1$ and $\dot{Q}_1$ were varied ($\dot{Q}_2$ adjusted to maintain the sum of all $\dot{Q} = 1$) and the best match determined over a range of shunt (fig. 4, table I). The arterial blood-gas tensions from the above distribution can be matched with distributions containing 0–10% shunt, although the match is best with distributions ranging from 1 to 7% shunt. The arterial blood-gas tensions could not be matched with pure shunt without a low-$\dot{V}_A/\dot{Q}$ compartment. The important thing to note is that

TABLE II. *Comparison of arterial blood-gas tensions with 10% shunt v. 5% shunt and 5% perfusion at* $\dot{V}A/\dot{Q} = 0.1$. *RQ = 0.85;* $(Ca_{O_2}-C\bar{v}_{O_2}) = 5$ *ml dl*$^{-1}$*; tracheal* $PI_{O_2} = 150$ *mm Hg (20 kPa)*

Shunt	Perfusion at $\dot{V}A/\dot{Q} = 0.1$	Perfusion at $\dot{V}A/\dot{Q} = 0.8$	Pa_{CO_2} (mm Hg)	Pa_{CO_2} (kPa)	Pa_{O_2} (mm Hg)	Pa_{O_2} (kPa)	pHa
0.10	0	0.9	45.5	6.05	76.6	10.2	7.36
0.05	0.05	0.9	45.1	6.0	78.9	10.5	7.36

all the matches contain 12.9–16.5% shunt plus low-$\dot{V}A/\dot{Q}$.

Table II compares the arterial blood-gas tensions of two bipartite distributions, differing only in that one contains 10% shunt, and the other contains 5% shunt and 5% perfusion at $\dot{V}A/\dot{Q} = 0.1$. The blood-gas tensions of the two distributions are indistinguishable. Thus the arterial blood-gas tensions cannot fully resolve shunt from low-$\dot{V}A/\dot{Q}$ compartments; however, the total amount of shunt plus low-$\dot{V}A/\dot{Q}$ can be determined.

Relationship of arterial blood-gas tensions to bipartite (shunt and one other compartment) variables

The retentions of patient No. 1 (Wagner et al., 1978; Lee, Patterson and Kaufman, 1987) are indistinguishable from those of the bipartite distribution: shunt = 0.0408; $\dot{V}A/\dot{Q}]_1 = 0.66$, $\dot{Q}_1 = 0.9592$. Using this distribution, the arterial blood-gas tensions were calculated. The resulting Pa_{CO_2} and Pa_{O_2}, with a tracheal PI_{O_2} of 150 and 350 mm Hg (20 and 46.6 kPa) are represented by the heavy horizontal lines in figure 5A and B, respectively. Assume we do not know the distribution from which these arterial blood-gas values resulted. A first attempt is to see whether a matching bipartite distribution can be found. The Pa_{CO_2} is determined almost completely by the $\dot{V}A/\dot{Q}$ of the ventilated compartment. The effect of shunt on Pa_{CO_2} is negligible. Once the $\dot{V}A/\dot{Q}$ is fixed, enough shunt is added to adjust the Pa_{O_2} to the desired value. A higher tracheal PI_{O_2} increases the slope of the Pa_{O_2} v. shunt line.

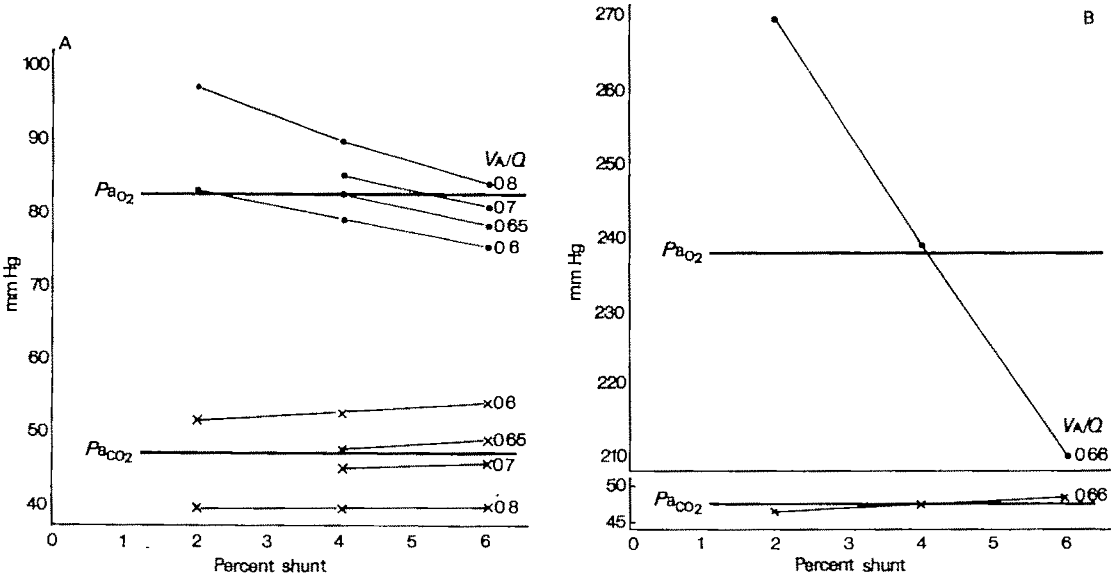
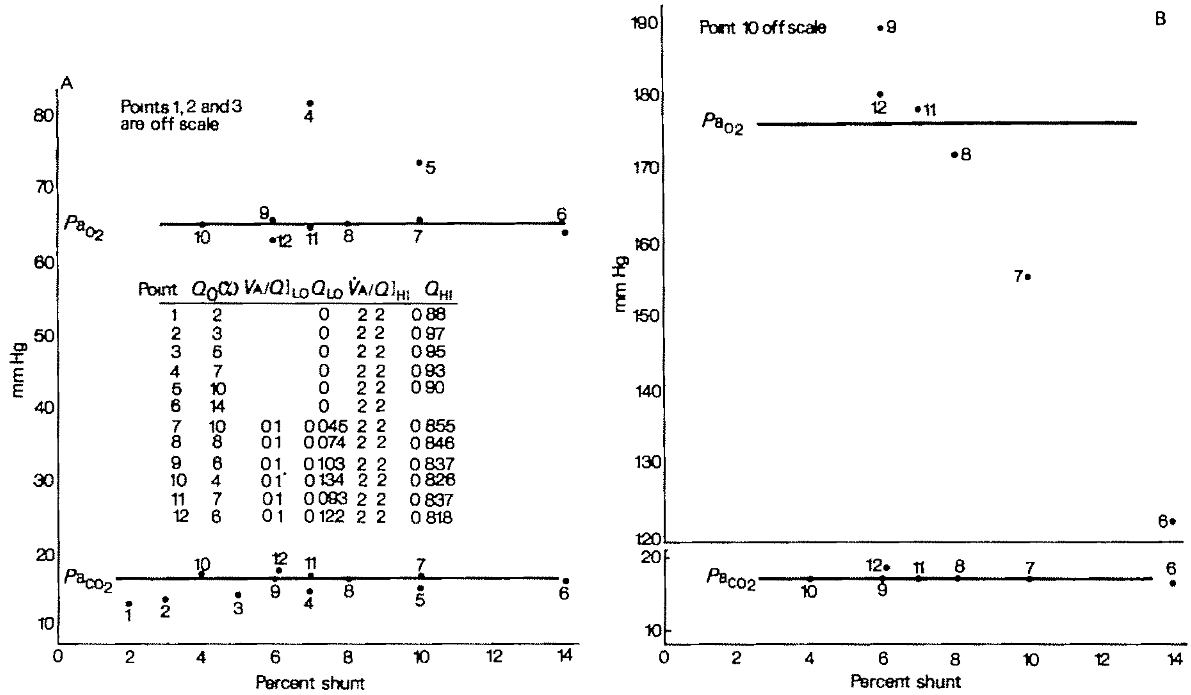


FIG. 5. The variation of arterial blood-gas tensions with shunt and $\dot{V}A/\dot{Q}$ in a bipartite distribution. The vertical positions of the bold lines represent the arterial blood-gas tensions of the distribution: shunt = 4.08%, $\dot{V}A/\dot{Q} = 0.66$. A: Tracheal $PI_{O_2} = 150$ mm Hg (20 kPa); B: tracheal $PI_{O_2} = 350$ mm Hg (46.6 kPa).



Point	Q_0(%)	$V_A/Q]_{LO}$	Q_{LO}	$\dot{V}_A/Q]_{HI}$	Q_{HI}
1	2		0	2.2	0.88
2	3		0	2.2	0.97
3	6		0	2.2	0.95
4	7		0	2.2	0.93
5	10		0	2.2	0.90
6	14		0	2.2	
7	10	0.1	0.046	2.2	0.855
8	8	0.1	0.074	2.2	0.846
9	6	0.1	0.103	2.2	0.837
10	4	0.1	0.134	2.2	0.826
11	7	0.1	0.093	2.2	0.837
12	6	0.1	0.122	2.2	0.818

FIG. 6. The variation of arterial blood-gas tensions with shunt and $\dot{V}A/\dot{Q}]_{LO}$ in a tripartite distribution. The vertical positions of the bold lines represent the arterial blood-gas tensions of the distribution: shunt = 3%, $\dot{V}A/\dot{Q}]_{LO} = 0.061$, $\dot{Q}_{LO} = 0.1261$ and $\dot{V}A/\dot{Q}]_{HI} = 2.2$, $\dot{Q}_{HI} = 0.8439$. A: Tracheal PI_{O_2} = 150 mm Hg (20 kPa); B: tracheal PI_{O_2} = 350 mm Hg (46.6 kPa).

Relationship of arterial blood-gas tensions to tripartite (shunt and two other compartments) distribution parameters

Assume we have a set of arterial blood-gas tensions from which we have failed to find a matching bipartite distribution. We replace the single ventilated compartment by two compartments in the trial distribution. We perturb the position and perfusions of the compartments to arrive at a match.

The Pa_{CO_2} is determined primarily by the well ventilated compartment, so the approximate $\dot{V}A/\dot{Q}$ of this compartment can be estimated relatively accurately. Figure 6A is an attempt to match the arterial blood-gas tensions resulting from a tripartite distribution. These tensions cannot be matched by a bipartite distribution. It is the same distribution discussed in the section "shunt *v.* low $\dot{V}A/\dot{Q}$". The bipartite distribution 6, containing 14% shunt and only one ventilated compartment, would appear to be a good match. The tripartite distributions 7–12 also appear to be good matches. Figure 6A is calculated with a tracheal PI_{O_2} of 150 mm Hg (20 kPa). Figure 6B shows distributions 6–12 calculated with a tracheal PI_{O_2} of 350 mm Hg (46.6 kPa). Distribution 11 is the best match, although distributions 8 and 12 are acceptable. In general, it is possible to determine a large number of tripartite fits for an arterial blood-gas tension at one tracheal PI_{O_2}. Requiring the match to satisfy two tracheal PI_{O_2} values limits the solution to a narrow range. The total shunt plus low-$\dot{V}A/\dot{Q}$ perfusion of distributions 8, 11 and 12 range from 15.4 to 18.2%. Thus, as figure 4 shows, the exact mix of shunt and low-$\dot{V}A/\dot{Q}$ perfusion of a tripartite distribution cannot be resolved by arterial blood-gas tensions; however, the total shunt plus low-$\dot{V}A/\dot{Q}$ perfusion can be determined within fairly narrow limits. Placing distributions 8, 11 and 12 on figure 4 demonstrates that acceptable matches lie within a band on each side of the plotted line.

Convergence of multiple inert gas method and blood-gas method

The bipartite and tripartite distributions determined from the published retentions of patients Nos 1 and 2 (Wagner et al., 1978; Lee, Patterson and Kaufman, 1987) were modified by the addition of 2% additional shunt. The additional shunt was to take into account the non-pulmonary shunt that the multiple inert gas method does not measure. The reported respiratory quotient and arterial blood-gas tensions (entered to the program as starting values for mixed-venous blood-gas tensions) for each patient were entered to the program along with the modified distribution. Since the $(Ca_{O_2}-C\bar{v}_{O_2})$ of the patients were not reported, we then tried different $(Ca_{O_2}-C\bar{v}_{O_2})$ values to see if the model could reproduce the reported arterial blood-gas values. The reported values for patient No. 1 were $Pa_{CO_2} = 34$ mm Hg (4.52 kPa), $Pa_{O_2} = 93$ mm Hg (12.4 kPa), $pH_a = 7.45$. At $(Ca_{O_2}-C\bar{v}_{O_2}) = 3.4$ ml dl^{-1}, the model generated arterial blood-gas values of $Pa_{CO_2} = 34.1$ mm Hg (4.54 kPa), $Pa_{O_2} = 92.8$ mm Hg (12.3 kPa), $pH_a = 7.45$ with $P\bar{v}_{CO_2} = 37.8$ mm Hg (5.03 kPa), $P\bar{v}_{O_2} = 44.5$ mm Hg (5.92 kPa), $pH_{\bar{v}} = 7.43$. Using the reported cardiac output of 6.3 litre min^{-1}, the oxygen consumption was 214 ml min^{-1}. The reported arterial blood-gas values for patient No. 2 were $Pa_{CO_2} = 26$ mm Hg (3.46 kPa), $Pa_{O_2} = 70$ mm Hg (9.31 kPa), $pH_a = 7.51$. At $(Ca_{O_2}-C\bar{v}_{O_2}) = 5.3$ ml dl^{-1}, the model generated arterial blood-gas tensions of $Pa_{CO_2} = 25.2$ mm Hg (3.35 kPa), $Pa_{O_2} = 68.3$ mm Hg (9 kPa), $pH_a = 7.52$ with $P\bar{v}_{CO_2} = 29.3$ mm Hg (3.9 kPa), $P\bar{v}_{O_2} = 33.6$ mm Hg (4.47 kPa), $pH_{\bar{v}} = 7.49$. The oxygen consumption was calculated from the reported cardiac output of 4.1 litre min^{-1} to be 217 ml min^{-1}.

Thus, the bipartite or tripartite distributions can be derived from the blood-gas tensions.

APPENDIX A

LIST OF ABBREVIATIONS

*	Fortran multiply
**	Fortran exponent
a–$\bar{v}$ diff	difference in concentration between arterial and mixed venous blood
BE	base excess
Ca_{CO_2}	concentration in arterial blood of CO_2 (ml dl^{-1})
CACO2C	concentration in alveolar capillary blood of CO_2 determined by continuity Eq. (ml dl^{-1}) (Fortran variable)
CACO2D	concentration in alveolar capillary blood of CO_2 determined by dissociation Eq. (ml dl^{-1}) (Fortran variable)
CAERR	error between CACO2C and CACO2D, present iteration
CAIERR	error between CACO2C and CACO2D at initial conditions or at one iteration before present
Ca_{O_2}	concentration of oxygen in arterial blood (ml dl^{-1})
$(Ca_{O_2}-C\bar{v}_{O_2})$	difference in concentration of O_2 in arterial and mixed venous blood (ml dl^{-1})
C_{blood}	concentration of CO_2 in blood (ml dl^{-1}), used in figure 10
C_{CO_2}	concentration of CO_2 in blood (ml dl^{-1})
CCO2	concentration of CO_2 in blood (ml dl^{-1}) (Fortran variable)
$C_{CO_2}]_i$	concentration of CO_2 (ml dl^{-1}) in capillary blood of *i*th compartment
C_{plasma}	concentration of CO_2 in plasma (ml dl^{-1}), used in figure 10
$C\bar{v}_{CO_2}$	concentration of CO_2 in mixed venous blood (ml dl^{-1})
$C\bar{v}_{O_2}$	concentration of O_2 mixed venous blood (ml dl^{-1})
CVCO2C	concentration of CO_2 in mixed venous blood determined by continuity Eq. (ml dl^{-1}) (Fortran variable)
CVCO2D	concentration of CO_2 in mixed venous blood determined by dissociation Eq. (ml dl^{-1}) (Fortran variable)
D	linear interpolation of DOX and DR for intermediate haemoglobin saturation
DELTCC	CAERR – CAIERR
DELTP	difference in P_{O_2}, present iteration and P_{O_2}, previous iteration
DELTPC	PACO2 – PACO2I
DELTS	SAERR – SAEIRR
$dHCO_3/dpH$	slope of HCO_3^- line in the HCO_3^- *v.* pH acid–base plot (mmol litre^{-1}/pH unit)
DOX	ratio of CO_2 concentration intracellular/extracellular, haemoglobin oxygenated
DR	ratio of CO_2 concentration intracellular/extracellular, haemoglobin without oxygen
EXPV	a function used to convert P_{O_2} to virtual P_{O_2} which is used in Kelman Eq. for haemoglobin saturation to adjust for varying temp., pH, P_{CO_2} (Fortran variable)
F_i	$\dot{V}_A/\dot{Q}$ of the *i*th compartment
g	empirical coefficient used iteratively to estimate a new pH
Hb	haemoglobin concentration
HCO3BL	buffer-line HCO_3^- in HCO_3^- *v.* pH plot (mmol litre^{-1})
Hct	haematocrit
PA_{CO_2}	alveolar partial pressure of CO_2 (mm Hg)
PA_{CO_2}	alveolar partial pressure of O_2 (mm Hg)
PACO2	alveolar partial pressure of CO_2, present iteration (mm Hg) (Fortran variable)
PACO2I	alveolar partial pressure of CO_2 at initial conditions or at previous iteration (mm Hg) (Fortran variable)
$PA_{CO_2}]_i$	alveolar partial pressure of CO_2 in the *i*th compartment (mm Hg)
Pa_{O_2}	arterial partial pressure of oxygen (mm Hg)
PA_{O_2}	alveolar partial pressure of O_2 (mm Hg)
$PA_{O_2}]_i$	alveolar partial pressure of O_2 in the *i*th compartment (mm Hg)
$Pa_{O_2}v$	virtual partial pressure of O_2 used to calculate haemoglobin saturation (mm Hg)

Pc_{CO_2}	alveolar capillary partial pressure of CO_2 (mm Hg)
P_{CO_2}	partial pressure of CO_2 (mm Hg)
PCO	partial pressure of CO_2 in alveolar capillary blood such that $\lvert CAERR \rvert < 0.1$
pH_a	arterial pH
pH_c	pulmonary capillary pH
(PH−PK)	difference between blood pH and H_2CO_3 pK (Fortran variable)
$pH_{\bar{v}}$	mixed venous pH
$P_{I_{CO_2}}$	partial pressure inspired CO_2 (mm Hg)
P_{initial}	the $P_{A_{O_2}}]_i$ that results in $S_{O_2}]_i = 1$ as calculated by Eq. (2)
$P_{I_{O_2}}$	partial pressure inspired O_2 (mm Hg)
P_{O_2}	partial pressure O_2 (mm Hg)
$P_{\bar{v}_{CO_2}}$	mixed venous partial pressure CO_2 (mm Hg)
PVCO2	mixed venous partial pressure CO_2 (mm Hg) (Fortran variable)
$P_{\bar{v}_{O_2}}$	mixed venous partial pressure O_2 (mm Hg)
$P_{\bar{v}_{O_2,v}}$	virtual partial pressure of O_2 in mixed venous blood used to calculate haemoglobin saturation (mm Hg)
RQ	respiratory quotient $\dot{V}_{CO_2}/\dot{V}_{O_2}$
SAC	haemoglobin saturation calculated from continuity Eq.
SAD	haemoglobin saturation calculated from dissociation Eq. (Kelman)
Sa_{O_2}	saturation of arterial haemoglobin
$S_{O_2}]_i$	saturation of haemoglobin in alveolar capillary blood of the *i*th compartment
SAERR	difference between alveolar capillary saturation calculated by continuity Eq. and dissociation Eq. (Kelman)
SAIERR	same as SAERR, but at initial conditions or at previous iteration
Sc_{O_2}	haemoglobin saturation of alveolar capillary blood
sl	estimated slope of line corresponding to plot of error between concentrations determined by continuity Eq. and dissociation Eq. (ordinate) and partial pressure of gas (abscissa)
SLOPEC	Sl for CO_2
S_{O_2}	saturation of oxygen in blood
SOL	solubility of CO_2
$S\bar{v}$	haemoglobin saturation in mixed venous blood
$S\bar{v}_{O_2}$	haemoglobin saturation in mixed venous blood
t	temperature (°C)
TAI	total arterial O_2 concentration (ml dl^{-1}) (including dissolved); initial estimate (Fortran variable)
T_{CO_2}	total arterial CO_2 concentration (ml dl^{-1})
TO2	total arterial O_2 concentration (ml dl^{-1}) (including dissolved) (Fortran variable)
$T_{O_2}]_i$	total O_2 concentration (ml dl^{-1}) (including dissolved) in capillary blood of the *i*th compartment

APPENDIX B

ALGORITHMS

Overall algorithm

At each F_i:

(1) Calculate virtual P_{O_2} at given temperature, initialize pH = pH_a, $P_{CO_2} = P_{\bar{v}_{CO_2}} - 6$.

(2) $P_{A_{O_2}}$ algorithm: calculate S_{O_2} and $P_{A_{O_2}}$. S_{O_2} is f(virtual $P_{A_{O_2}}$); virtual $P_{A_{O_2}} = f(P_{A_{O_2}}, \text{pH}, P_{CO_2}, t)$

(3) $P_{A_{CO_2}}$ algorithm: calculate C_{CO_2}, $P_{A_{CO_2}}$ using S_{O_2} from above. pH_c is initialized to = pH_a

(4) BE algorithm: calculate corrected (appropriate) pH_c.

New value for pH, P_{CO_2} to calculate virtual P_{O_2}

At pulmonary vein:

(5) Calculate Pa_{CO_2}, Pa_{O_2}, pH_a from Ca_{CO_2} and TO2, assuming BE constant.

Algorithm for finding $P_{A_{O_2}}]_i$, *given* F_i, $S\bar{v}_{O_2}$, $P_{I_{O_2}}$ *and* Hb

(1) For given $S\bar{v}$, $P_{I_{O_2}}$, Hb and F_i calculate $P_{A_{O_2}}]_i$ using Eq. (2) (below), assuming $S_{O_2}]_i = 1$. This $P_{A_{O_2}}]_i = P_{\text{initial}}$.
If $P_{\text{initial}} < 0$, set it = 0.
Calculate S_{initial} as $S_{O_2}]_i$ at P_{initial} with dissociation curve from Kelman.
Refer to figure 7.

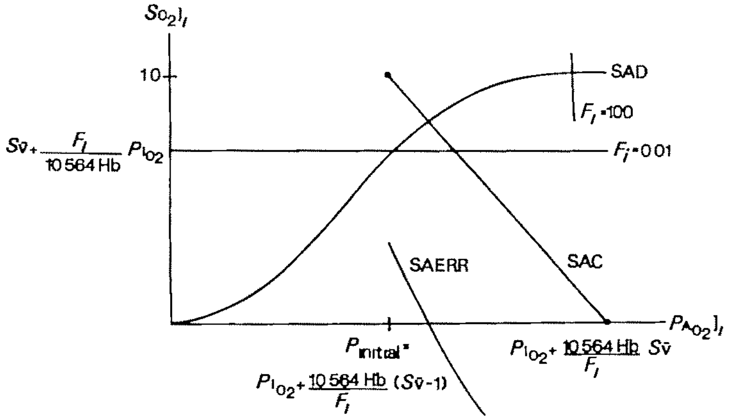

$S_{O_2}]_i$
1·0
$S\bar{v} + \frac{F_i}{10.564\,Hb} P_{I_{O_2}}$
SAD
$F_i = 100$
$F_i = 0.01$
SAERR
SAC
$P_{A_{O_2}}]_i$
$P_{\text{initial}} =$
$P_{I_{O_2}} + \frac{10.564\,Hb}{F_i}(S\bar{v} - 1)$
$P_{I_{O_2}} + \frac{10.564\,Hb}{F_i} S\bar{v}$

FIG. 7. Algorithm for calculating the P_{O_2} in the *i*th compartment from the simultaneous solution (point of intersection) of two equations of haemoglobin saturation. SAD is the oxygen dissociation curve, SAC is the function required by conservation of mass (continuity: O_2 in = O_2 out) and SAERR is the difference between them.

```
(2) Incrementally increase $P\text{A}_{\text{O}_2}]_i$ above $P_{\text{initial}}$ and calculate $S\text{o}_2]_i$ with Eq. (1) (see below) and standard dissociation curve (Kelman).
    (a) Calculate $(1-S_{\text{initial}})$, store as SAIERR.
    (b) Increment $P\text{A}_{\text{O}_2}]_i$ by 10 mm Hg.
    (c) Calculate saturation with continuity equation Eq. (1) (SAC) and dissociation equation (SAD) at $P\text{A}_{\text{O}_2}]_i$.
    (d) Calculate SAERR = SAC − SAD. If SAERR is between +0.001 and −0.001, then done.
(3) Calculate $P\text{A}_{\text{O}_2}]_i - P_{\text{initial}}$ = DELTP. Refer to figure 8.
    Calculate SAERR − SAEIRR = DELTS.
    Calculate DELTS/DELTP = sl.
    Calculate − SAIERR/sl + $P_{\text{initial}} = P_0$
    Set $P_{\text{initial}} = P\text{A}_{\text{O}_2}]_i$
    Set SAIERR = SAERR
    Set $P\text{A}_{\text{O}_2}]_i = P_0$
    Go to 2(c)
```

Continuity equation:

$$S\text{o}_2]_i = S\bar{v} + \frac{F_i P\text{I}_{\text{O}_2}}{10.564\ \text{Hb}} - \frac{F_i P\text{A}_{\text{O}_2}]_i}{10.564\ \text{Hb}}$$

$$= S\bar{v} + \frac{F_i}{10.564\ \text{Hb}}(P\text{I}_{\text{O}_2} - P\text{A}_{\text{O}_2}]_i) \qquad \text{Eq. (1)}$$

$$P\text{A}_{\text{O}_2}]_i = -\frac{10.564\ \text{Hb}}{F_i} S\text{o}_2]_i + P\text{I}_{\text{O}_2} + \frac{10.564\ \text{Hb}}{F_i} S\bar{v}$$

$$= \frac{10.564\ \text{Hb}}{F_i}(S\bar{v} - S\text{o}_2]_i) + P\text{I}_{\text{O}_2} \qquad \text{Eq. (2)}$$

Note: Eq. (2) is Eq. (1) solved for $P\text{A}_{\text{O}_2}]_i$

Algorithm for finding $P\text{A}_{\text{CO}_2}]_i$, given F_i, $S\text{o}_2]_i$, $S\bar{v}_{\text{O}_2}$, $P\bar{v}_{\text{CO}_2}$, pH_v, Hct, t. Refer to figure 9.

```
calculate $C\text{co}_2$ with dissociation Eq. (Kelman) and Eq. C at $P\bar{v}_{\text{CO}_2}$: CVCO2D, CVCO2C
calculate error CVCO2C − CVCO2D = CAIERR
set       PACO2I = PVCO2
decrease $P\text{co}_2$ by 10 mm Hg: PACO2 = PVCO2 − 10
┌→ calculate $C\text{co}_2$ with dissociation Eq. and Eq. C at PACO2:
│    CACO2D, CACO2C
│  calculate error CACO2C − CACO2D = CAERR; if CAERR
│    is between +0.1 and −0.1, then done.
│  calculate PACO2 − PACO2I = DELTPC
│            CAERR − CAIERR = DELTCC
│            SLOPEC = DELTCC/DELTPC
│            PCO = −CAIERR/SLOPEC + PACO2I
│  set       PACO2I = PACO2
│            CAIERR = CAERR
└─────────── PACO2 = PCO
```

Continuity equation:

$$C\text{co}_2]_i = C\bar{v}_{\text{CO}_2} - 0.1316\ P\text{A}_{\text{CO}_2}]_i F_i \qquad \text{Eq. C}$$

Calculation of total CO_2 *in capillary blood* at a given $S\text{c}_{\text{O}_2}$, pH_v, $P\text{c}_{\text{CO}_2}$, T, Hct

```
Initialize $\text{pH}_c = \text{pH}_a$ ($\text{pH}_a = \text{pH}_v + 0.04$)
┌→ $P\text{co}_2$ ALGORITHM: calculate $P\text{c}_{\text{CO}_2}$ at $F_i$, $S\text{c}_{\text{O}_2}$, $S\bar{v}_{\text{O}_2}$, $P\bar{v}_{\text{CO}_2}$,
│    $\text{pH}_v$, Hct, T
└─ BE ALGORITHM: calculate $\text{pH}_c$ appropriate for calculated
     $P\text{c}_{\text{CO}_2}$ and mixed venous gas tensions.
Calculate $C\text{co}_2]_i$. Refer to figure 10.
```

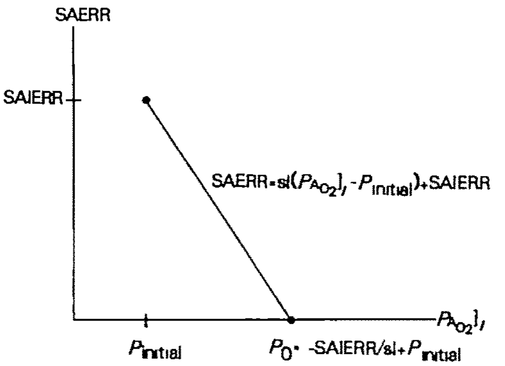


FIG. 8. Calculation of the P_0, at which SAERR = 0, the solution P_0. The calculation approximates SAERR as a linear function of $P\text{o}_2$.

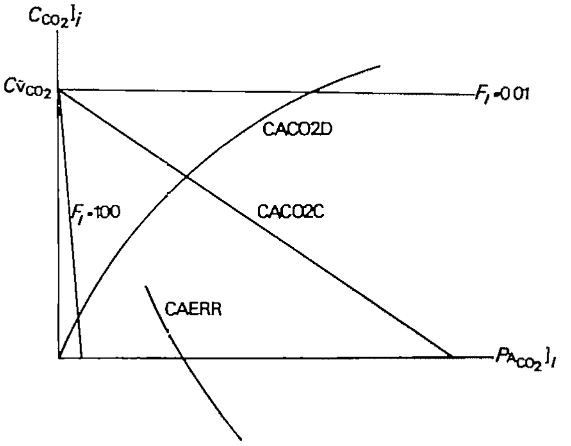


FIG. 9. Algorithm for calculating the $P\text{A}_{\text{CO}_2}$ in the ith compartment from the simultaneous solution (point of intersection) of two equations of carbon dioxide content of blood. CACO2D is the carbon dioxide dissociation curve, CACO2C is the function required by conservation of mass (continuity: CO_2 in = CO_2 out) and CAERR is the difference between them.

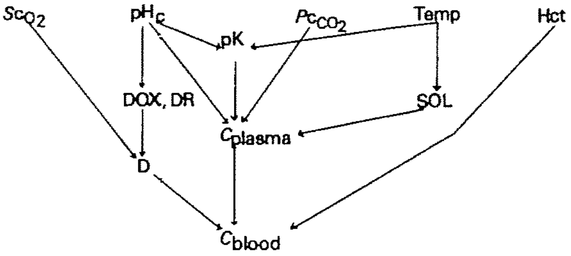


FIG. 10. Calculation of total blood carbon dioxide content (C_{blood}) in the alveolar capillary. Each variable is determined by all the variables at the origin of the arrows pointing towards it.

TABLE III. *At constant BE, EXPV is closely approximated by a function of pH only. pH and* P_{CO_2} *calculated with BE = O, Hb = 9 mmol litre*$^{-1}$ *from Siggaard-Andersen (Radiometer).* † *From Kelman EXPV = 0.4 (pH − 7.4) + 0.06 (log 40 − log* P_{CO_2}*) + f(t)*

	P_{CO_2}			
pH	(mm Hg)	(kPa)	EXPV†	0.495 (pH − 7.4)
7.1	118	15.7	−0.1482	−0.1485
7.2	83	11.8	−0.0990	−0.0990
7.3	58	7.7	−0.0497	−0.0495
7.4	40	5.3	—	0
7.5	28	3.7	0.0493	+0.0495
7.6	19.5	25.9	0.0987	+0.0990
7.7	13.5	18.0	0.1483	+0.1485

Base excess (BE) algorithm

```
Initialize $pH_c = pH_a$
find $Pa_{CO_2}$ (name it 'P') from $P_{CO_2}$ algorithm
calculate concentration of $HCO_3$ at 'P', i.e. at $Pa_{CO_2}$, $pH_a$
calculate concentration of $HCO_3$ at $pH_a$ from buffer line
(determined by mixed venous blood gases and $S_{CO_2}$)
calculate base excess error, BERR; if BERR is between
+0.1 and −0.1, then done
calculate new $pH_c$ = old pH − g (BERR) where g is approximately 0.025
```

Algorithm for calculating Pa_{CO_2}, Pa_{O_2} *from* Ca_{CO_2}, Sa_{O_2} (BE constant)

```
calculate CCO2 in pulmonary vein from $C_{CO_2}]_i$
Initialize $pH_a = pH_{\bar{v}}$, $Pa_{CO_2} = P\bar{v}_{CO_2}$
calculate total $CO_2$ ($T_{CO_2}$) at $pH_a$ and $Pa_{CO_2}$
compare $T_{CO_2}$ with CCO2; done, if difference less than 0.1, or
else generate new $pH_a$
calculate HCO3BL at new $pH_a$
calculate appropriate $Pa_{CO_2}$; $Pa_{CO_2}$ = HCO3BL/SOL*10**
(PH−PK)
calculate TO2 in pulmonary vein from $T_{O_2}]_i$
initialize $Pa_{O_2} = 40$
calculate virtual $Pa_{O_2}$
calculate total $O_2$ (TAI) at $Pa_{O_2,V}$
compare TAI with TO2; done, if difference less than 0.01, or
else generate new $Pa_{O_2,V}$
```

Body loop

```
Calculate a–$\bar{v}$ diff for $O_2$, $CO_2$
Compare with desired a–$\bar{v}$ difference
If $O_2$ is OK, go to $CO_2$ comparison
If $O_2$ is not OK, generate new $P\bar{v}_{O_2}$
If $CO_2$ is OK, done; proceed to calculate arterial gases
If $CO_2$ is not OK
   calculate new $pH\bar{v}$
   calculate new $P\bar{v}_{O_2,V}$, $S\bar{v}_{O_2}$ at new pH (table III)
   calculate new $HCO_3$ at new pH, saturation
   calculate new $P\bar{v}_{CO_2}$, maintain BE constant
Calculate $S\bar{v}_{O_2}$ at new $pH_{\bar{v}}$, $P\bar{v}_{CO_2}$; should be very close to
   $S\bar{v}_{O_2}$ found three calculations above
Calculate new $C\bar{v}_{CO_2}$ (CVCO2D) and $C\bar{v}_{O_2}$
Calculate new end-capillary gases (distribution same), and
   new arterial concentrations.
Re-initialize mixed venous gases for next distribution.
```

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GENERAL ANAESTHESIA FOR CARBON DIOXIDE LASER SURGERY WITHIN THE AIRWAY

A Review

M. L. PAES

SUMMARY

Carbon dioxide laser surgery in the airway presents the anaesthetist with new problems. The mode of action of carbon dioxide lasers and its effects on anaesthetic agents and equipment are described. Complications, especially of fire hazards in the airway, and methods of avoiding them are set out in detail. Various anaesthetic techniques for both laryngeal and tracheobronchial laser surgery are described.

Obstructive lesions of the airway always present difficulties in management and treatment, partly because of inadequate instrumentation and partly because of the sharing of the airway between anaesthetist and surgeon. An improvement in instrumentation, both surgical and anaesthetic, has permitted some progress. The introduction of carbon dioxide lasers has produced a significant advance in the management of oral cavity and airway lesions. The technique is especially useful in the paediatric airway where the avoidance of oedema and the need for minimal scarring is most critical (Healy, McGill and Strong, 1978).

The carbon dioxide laser produces a non-ionizing, invisible radiation in the far infra-red region of the light spectrum with a wavelength of 10.6 µm. The beam emanating from the laser generator consists of parallel waves of a single wavelength which is predictable and consistent. These waves can be focused by an appropriate lens to a point which contains energy capable of vaporizing biological tissue without inflicting thermal damage to adjacent tissue. The power needed to ablate tissue varies with the composition of the tissue.

Carbon dioxide laser radiation is almost completely absorbed by all biological tissue, irrespective of pigmentation. Tissue destruction is, in part, proportional to its water content. The destructive mechanism is entirely a thermal process resulting in a graded response of coagulation, carbonization and vaporization of tissue, dependent on the amount of energy absorbed. Carbon dioxide laser beams penetrate only the initial 200 µm of tissue and produce very precise, clean incisions with little surface bleeding or damage to adjacent tissue. Small blood vessels are coagulated instantly so that visibility is not affected by a spattering of blood flecks. There is minimal postoperative oedema, with rapid pain-free healing and little scarring even after extensive resection. It is an appropriate instrument for excision and ablation of tissue. The carbon dioxide laser beam is invisible so, in order to aim, a helium–neon aiming beam is used as a marker. The two beams must be coaxial to avoid damage to structures outside the target area.

However, there are limitations. The carbon dioxide beam cannot be transmitted through optical fibres, but is manipulated by a system of mirrors and prisms to reach the target area which makes the system awkward to use. It is imperative that the lesion is clearly visible at all times during the vaporization process. It may be possible to deflect the beam round corners with the aid of a mirror or a highly polished surface. The operative field must be dry, as the presence of blood, saliva and other fluids not only reduces the amount of energy reaching the target, but may also affect the optical system, making it difficult to proceed. However, the greatest concern lies in the inherent risk of introducing a high temperature source to

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M. L. PAES, F.F.A.R.C.S., Regional Cardiothoracic Centre, Freeman Hospital, Freeman Road, High Heaton, Newcastle-upon-Tyne NE7 7DN. Accepted for Publication: July 27, 1987.

the airway. The anaesthetic risk is greater than all others and should be of concern to both anaesthetist and surgeon.

CARBON DIOXIDE LASERS AND ANAESTHESIA

With the rapid advancement of laser technology and its widespread use in surgery, the anaesthetist is presented with new problems. These should be considered in depth before embarking on the use of lasers in the airway.

Competition for the airway

Anaesthetic management for laryngeal surgery presents many problems arising from the conflicting needs of the anaesthetist and surgeon for control of the airway—which may already be compromised by disease (Norton et al., 1976; Edelist and Alberti, 1982). Neither has complete control, and this may lead to a degree of insecurity on both sides. The quality of work may be impaired as a result of difficulty with ventilation and inadequate operating conditions. In view of the narrow margins of safety, the ultimate success of any procedure will depend on close co-operation. Better, and more consistent, results will be produced by a team which works together for a period of time.

Circulatory changes

Tracheal instrumentation with a rigid endoscope is consistently associated with tachycardia and hypertension. Some patients may exhibit ECG changes of myocardial ischaemia (Edelist and Alberti, 1982; Conacher, Paes and Morritt, 1987). These responses persist for the duration of the intubation and are not usually obtunded by the use of analgesic agents. In patients with angina, pre-treatment with beta-adrenoceptor blocking agents, vasodilator therapy or both, where required, may alleviate these changes during the procedure. Cardiac arrythmias may appear in the presence of hypoxia and hypercapnia—neither of which is uncommon.

Airway impedance

The majority of lesions requiring laser surgery in the airway, either malignant or benign, are obstructive in nature. They increase the impedance of the airway—the magnitude of the increase depending on the degree of obstruction and the extent of the lesion. Respiratory workload is usually high and associated with an ineffectual cough mechanism. Removal of tracheobronchial secretions may be hampered, and be followed by an increased incidence of pulmonary atelectasis and bacterial infection. In patients with compromised airways, a variety of laryngoscope blades, tracheal tubes and bronchoscopes must be available. A surgeon capable of performing a tracheotomy must be in attendance.

Integrity of the airway

There are occasions for laryngeal surgery when the anaesthetic gases are transported through narrow-lumen tracheal tubes. This permits the surgeon to examine and operate on lesions in the airway by working around the tube. Hyperextension of the neck or side-to-side movement of the head may obstruct the tube or gas hoses.

Choice of anaesthetic agents

Because of the intense heat generated, lasers must not be used with flammable agents. Nitrous oxide, although not flammable, does support combustion at high temperatures and should be avoided with open anaesthetic systems. The oxygen concentration should be as low as possible commensurate with adequate oxygenation. A concentration of 25–30% is invariably used. The incidence of "flaring" of carbonized tissue increases as the oxygen concentration at the operation site increases, as well as with the continuous use of the laser.

Volatile agents are the mainstay of anaesthesia during laryngeal surgery. As most of these patients require frequent surgery, the repeated use of halothane should be avoided.

Continuous i.v. anaesthesia has considerable advantage, especially in conjunction with jet ventilation. Recovery is rapid and operating room pollution is avoided.

Fire hazards

With increased use of lasers in the airway, sporadic incidents of tracheal tube ignition, causing burns of the laryngotracheal tissue, have been reported. The intense heat generated by a carbon dioxide laser can ignite most non-metallic and non-glass objects unless they are protected from direct or reflected laser beams. The ease with which this occurs depends on the material, environmental gas composition, duration of exposure and the power of the laser. The incidence of damage to an unprotected tube by direct exposure to the beam is high even in experienced hands (Snow and Norton, 1975; Vourc'h, Tannières and Freche, 1975; Snow et al., 1976). On direct exposure to a laser in an environment of 25% oxygen, red rubber is more resistant than PVC. When the concentration of oxygen is increased, red rubber burns with little smoke, but PVC produces dense smoke, molten debris and the flame burns with an increasing intensity which is propagated along the flow of gases (Patel and Hicks, 1981). Red rubber and PVC tubes ignite in 100% oxygen, 100% nitrous oxide or any combination of the two (Wainwright, Moody and Carruth, 1981). Hence, the use of 25% oxygen in air or 25% oxygen in nitrogen is advocated instead of nitrous oxide.

A burn-resistant anaesthetic gas conduit is mandatory for laser surgery in the airway. A variety of methods to minimize the risk of ignition of the tubes is available, including the use of non-combustible materials.

The original method of protecting tracheal tubes involved the use of self-adhesive, non-reflective aluminium tape. The tube is carefully wrapped with the tape in a spiral fashion with overlapping edges, commencing just above the cuff or at the distal tip in uncuffed tubes and ending at the level of the uvula. The tape edges are then smoothed to decrease injury to pharyngeal and laryngeal tissue. This significantly retards ignition of both red rubber and PVC tubes. Although adequate, it is not without danger. Narrow tubes can become occluded as a result of compression by the foil as it accomodates to the curvature of the pharynx (Patil, Stehling and Zander, 1979). The tape does not always adhere adequately to the tube and may loosen or break off, resulting in acute airway obstruction (Kaeder and Hirshman, 1979). The outer wall of the tube is protected, but the cuff and the distal end of the tube can be ignited by direct or indirect contact with the laser beam (Burgess and LeJeune, 1979; Cozine et al., 1981). The inner wall of the tube may also be set alight by incandescent tissue debris floating into the lumen of the tube (Hirshman and Smith, 1980). The cuff, when ruptured, allows a massive leak of anaesthetic gases, leading to hypoventilation as well as providing a richer environment for ignition of the tube (Konchigeri and Shaker, 1974). The cuff can be protected by placing saline-soaked cottonoids around it and these are kept moist throughout the procedure. A metal wire attached to the cottonoid is a reminder for its removal.

One inexpensive modification is to wrap the tube with muslin in a fashion similar to the aluminium tape (Patil, Stehling and Zander, 1979; Kumar and Frost, 1981). The tube is immersed in saline before insertion and kept moist by periodically wetting the muslin. There is no reflection of the beam and "hot spot" burning of surrounding tissue by hot aluminium tape.

Laser-Shield cuffed tracheal tubes made from silicone and having an outer coating of metallic oxide, are more resistant to lasers than red rubber and PVC tubes. However, the cuffs of these tubes do present a hazard when inflated with air; multiple impacts from a laser will penetrate the cuff, which could ignite. Hence, the cuff is inflated with ice-cold saline, which acts as a heat sump to dissipate the heat from the beam. Persistent contact will perforate the saline-filled cuff without ignition (Rubiano et al., 1985). These tubes do burn in high oxygen concentrations, are expensive and are for single use only. The high volume, low pressure floppy cuff may present difficulty during its passage through a narrow larynx.

The development of a flexible metal tube provides a partial solution to the problem (Norton and De Vos, 1978; Hirshman et al., 1980; Hunton and Oswal, 1985). All the flexometallic tubes in use are non-combustible, easily sterilized, gas tight and non-reactive with human tissue. They should be atraumatic, but the possibility remains of damage to the cords during insertion. An outer, split red rubber sleeve will help to smooth introduction but should be removed before laser vaporization. The metal tube is uncuffed and should be used with a high gas flow or an injector to provide adequate ventilation. Wet cottonoids can be placed around the tube to act as a pack, as well as a protective shield for normal tissue distal to the lesion. The walls of these tubes are relatively thick, with a large external diameter which precludes their use in the younger patient. They may be reused many times and provide long-term economy.

Effects on the airway. The effects of an explosion in the airway depend on the magnitude of the event and the severity of the burn. Two types of burn injury are produced by laser explosions. The thermal effect from dry heat dissipated by vaporization of cellular and surface water gives rise to a mummified appearance of the tissue. The second type of injury arises from the chemical response of tissues to toxic PVC fumes. Prompt and appropriate management is facilitated if the operating team have discussed and rehearsed their response. Schramm, Mattox and Stool (1981) have suggested the following regimen in the management of airway explosions. I acknowledge with thanks the authors, and the editor of *Laryngoscope*, for permitting me to use the following extract from their article:

> "*Primary emergency care*
>
> Stop ventilation, disconnect oxygen and remove endotracheal tube. Place oral airway and ventilate with anaesthesia mask.
>
> *Secondary emergency care*
>
> Perform rigid bronchoscopy to remove large foreign bodies, and lavage to trachea. Fibreoptic bronchoscopy to visualise small airways, remove small foreign bodies and lavage to distal airways.
>
> Evaluate injury to laryngo–tracheobronchial tree. Remove fragmented mucosa and debris. If necessary, perform a low tracheostomy.
>
> *Tertiary emergency care*
>
> Administer antibiotics and short term steroids. Provide a high humidity environment and positive end expiratory pressure ventilation, where necessary.
>
> *Subsequent management*
>
> Place patient in reverse isolation. Culture tracheal aspirate daily. Perform endoscopy 3–5 days postburn to evaluate extent of injury.
>
> Perform ventilation–perfusion studies and tomography of the respiratory tree.
>
> Early weaning of ventilation. If extubation not possible, replace tracheostomy tube with a Montgomery T tube."

This overall approach should be followed in the treatment of airway burns, although the individual steps may be managed differently according to the patient's needs.

In anterior lesions of the tongue and around the lips, a nasotracheal tube is used, with moist gauze packs in the mouth. Other lesions in the mouth and pharynx require a laserproof tracheal tube.

Damage to normal tissue

Turbulent gas flow during laser vaporization may cause vibration of the cords and tracheal walls as well as deflection of the laser beam. Normal structures away from the operative site may be damaged inadvertently from an overshoot or deflection of the beam, causing a laryngotracheal tear. Ideally, vaporization should occur during a quiescent ventilatory period, but synchronization of vaporization and ventilation is difficult (Schramm, Mattox and Stool, 1981). A technique which permits the anaesthetist and surgeon to take turns at the airway, will provide a quiet relaxed field, making the lesion an easy target (Conacher, Paes and Morritt, 1985; Paes, Conacher and Snellgrove, 1986).

The alignment of the aiming and vaporizing beams should be verified before every procedure. Malalignment of these beams will cause damage to adjacent structures.

Normal tissue can also be traumatized by unexpected coughing or movement (Birch, 1973; Snow et al., 1974). Proper maintenance of anaesthesia and the timely administration of a neuromuscular blocking drug are required. An increase in intrathoracic pressure in the presence of a laryngotracheal tear may result in pneumomediastinum, pneumothorax or pneumopericardium (Ganfield and Chapin, 1982; Vourc'h, Le Gall and Colchen, 1985).

Reflection of the beam from a mirror-like surface alters the direction of the beam without changing its properties. Thus the whole power of the beam is directed to an unintended area. Because carbon dioxide laser beams are absorbed within the first 200 μm of tissue, they are a hazard to the cornea. Corneal damage is prevented by insisting that all operating room personnel wear safety spectacles appropriate for the laser in use. The patient's eyes are protected by keeping the eyelids closed and covered with eyepads. Damage to distant sites such as the skin is slight because of the rapid decrease in laser energy beyond the focal point of the laser (Andrews and Moss, 1974; Hermens, Bennett and Hirshman, 1983). When lasers are in use, conspicuous notices to this effect should be placed outside each entrance of the theatre.

Pollution

Laser energy increases the temperature of intracellular water to boiling point instantly, causing rupture of the cell membrane and release of steam. Cell debris carbonizes and burns with a flare, and smoke is produced. Smoke particles may produce bronchospasm, alveolar oedema and diffuse atelectasis. In closed anaesthetic systems smoke is not transmitted to the alveoli, and its aspiration with an operating room suction apparatus improves the operator's view. In open anaesthetic systems, a compensatory high gas flow or jet ventilation tends to propel smoke forward to the distal airways. Application of suction close to the oral cavity or point of smoke production reduces alveolar pollution as well as the concentration of anaesthetic vapours (Rita, Seleny and Holinger, 1983). A technique of alternate phasing of ventilation and vaporization/suction reduces pollution in tracheobronchial surgery.

Pollution of the operating room environment with anaesthetic vapours and smoke can be minimized by using suction channels on layrngoscopes and bronchoscopes.

ANAESTHESIA FOR LARYNGEAL SURGERY

The single greatest medical use of the carbon dioxide laser is in surgery of the larynx. The precision, rapid healing and absence of oedema following laser surgery of the larynx are superior to conventional techniques. Nodules, polypi, granulomas and vocal cord oedema are treated with good results. In juvenile papillomatosis, the carbon dioxide laser enables the surgeon to remove all visible disease with precision, no oedema and minimal scarring. The need for tracheotomy has been virtually eliminated in these patients (Carruth, 1983). Laryngeal webs may be reduced in size following two to three treatments.

Preoperative assessment is always necessary. The degree of airway obstruction and the adequacy of ventilation must be carefully assessed. The quality of voice, ventilatory pattern and pulmonary function tests give a clue to the degree of ventilatory obstruction. Tomography and CT scans provide further information on anatomical changes in the airway (Rita, Seleny and Holinger, 1983).

Premedication is important, particularly in patients with papillomatosis requiring multiple exposures to laser surgery. A tranquillizing agent should be used in conjunction with an antisialagogue in the form of atropine, hyoscine or glycopyrrolate. The presence of orotracheal secretions may interfere with the smooth running of the procedure. Narcotic premedication is avoided if anaesthesia is dependent on spontaneous ventilation (Brummitt, Fearon and Brauma, 1981); many teams operate on unpremedicated patients.

Anaesthesia should be of a level adequate to avoid laryngospasm, but light enough for rapid recovery. The maintenance of adequate ventilation is the most important consideration to any anaesthetic technique for laser surgery on the larynx. A number of anaesthetic techniques have been described which can be grouped according to the type of gas conduit used. They consist of the use of: narrow-lumen tracheal tubes; jet ventilation; insufflation anaesthesia; any combination of the above.

Anaesthesia using narrow lumen tracheal tubes

In adults and children with i.v. access, anaesthesia is induced with thiopentone, and neuromuscular blockade achieved with a single dose of suxamethonium. In children without i.v. access, anaesthesia is produced by an inhalation induction using oxygen, air and a volatile agent followed by suxamethonium. A laserproof tube is inserted and loosely anchored to the left corner of the mouth. The tube selected is the widest that will pass through the lesion, but as a rule a 3.0-mm uncuffed tube in children and a 6.0-mm cuffed tube in adults will suffice. Anaesthesia is maintained by positive pressure ventilation using oxygen, air and a volatile agent. Further neuromuscular blockade is produced by intermittent doses of a short-acting non-depolarizing myoneural blocker or a continuous infusion of suxamethonium. Methyl prednisolone is sometimes given at induction to prevent tissue oedema from

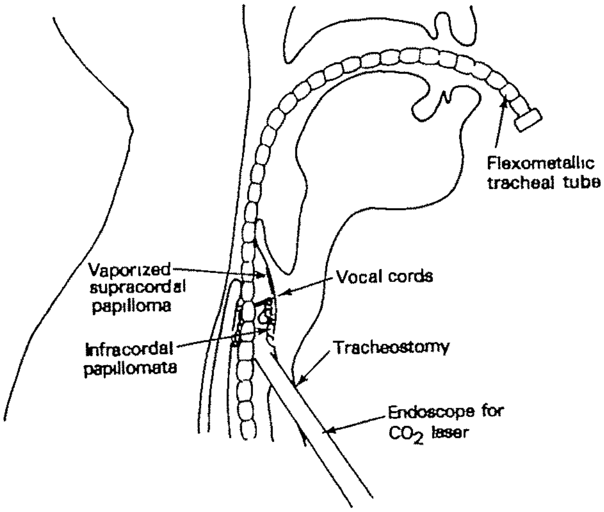
Flexometallic tracheal tube
Vaporized supracordal papilloma
Vocal cords
Infracordal papillomata
Tracheostomy
Endoscope for CO_2 laser

FIG. 1. Approach to infracordal papilloma through tracheostomy.

instrumentation, especially in tracheobronchial lesions (Snow and Norton, 1975). Care is taken to protect the patient's eyes, and a thick layer of damp "gamgee" having a central hole for access to the airway, is placed over the face.

The larynx is exposed with a suspension laryngoscope and the operating microscope with the laser attachment is subsequently attached following laryngoscopy. The position of the tracheal tube varies with the site of the lesion. It is placed anteriorly between the laryngoscope and the epiglottis for lesions in the interarytenoid area, whereas a posterior position gives a good view of the whole length of the vocal cords. If the patient presents with a tracheostomy, the problem of competition for the airway does not arise. A non-fenestrated metal tracheostomy tube or a laserproofed PVC tracheostomy tube is inserted through the stoma and anaesthesia maintained through it. A third alternative is to insert a red rubber tube through the lumen of a silver tracheostomy tube. The surgeon now commands the operating field, but care should be taken to protect the normal tissue and anaesthetic conduit by packing with wet cottonoids.

In patients with laryngeal papillomata and a tracheostomy, the supracordal lesions are easily vaporized via the pharyngeal approach. The infracordal and tracheal papilloma are more difficult to remove. If laser resection is through the tracheal stoma following removal of the tracheostomy tube, ventilation can become a problem. Laserproofed tubes are hazardous in this situation, as the inner surface and anaesthetic gases are exposed to the laser. A flexometallic tube passed through the vocal cords will allow adequate ventilation and surgical access, provided the larynx is large enough to accept the tube (fig. 1).

Following surgery, anaesthesia is discontinued, residual neuromuscular blockade antagonized and humidified oxygen provided in the recovery room. A feature of laser surgery is rapid, painfree healing, and the only discomfort arises from instrumentation of the airway.

The advantage of this technique of sharing the airway is its simplicity and familiarity to all anaesthetists. The airway is protected, allowing ventilation to proceed unimpeded, and the cuff prevents aspiration of blood and debris. The disadvantage lies in the possibility of tube ignition and partial obstruction of the surgeon's view by the tube.

Monitoring during anaesthesia consists of the use of a pulse oximeter, electrocardiograph and non-invasive measurements of arterial pressure. Rarely would blood-gas analysis be required for laryngeal surgery, but a transcutaneous oxygen electrode maybe useful in children.

Jet ventilation

In 1967, Sanders introduced the jet injector technique of ventilation for diagnosis and surgery of the upper airway. Ventilation using this technique provides excellent operating conditions for microsurgery of the larynx, with an unparalleled view and access to the respiratory tree as a result of the absence of the tracheal tube.

A high velocity jet of oxygen directed through the laryngoscope entrains room air, resulting in a large volume of an oxygen–air mixture being transmitted to the lungs. Various sizes of venturi needles are used, but they should be of a length such that the tips lie just beyond the vocal cords. A 16-gauge needle for paediatric patients and a 14-gauge needle for adults are usually used in conjunction with a jet ventilator or "Speedaire Blogun". The addition of a reducing valve to either device enables the anaesthetist to alter the working pressure to a value adequate to ventilate the patient without the risk of barotrauma.

The use of jet ventilation demands close observation and communication between anaesthetist and surgeon. Any difficulty in ventilation should be investigated immediately. Variations in driving pressure or alteration in direction of the jet produce marked variations in gas flow (Brummitt, Fearon and Brauma, 1981).

Pneumothorax, in association with an inadvertent laryngotracheal tear, has been reported at intervals. Barotrauma can also occur in large laryngeal lesions, which may produce a ball valve obstruction secondary to jet ventilation, resulting in increased intrathoracic pressure and subsequent pneumothorax (Oliverio et al., 1979; Ruder et al., 1981). Distension of the stomach is a possibility if the jet nozzle is displaced to a position proximal to the larynx (Chang et al., 1978). Measures for decompression should be used especially in children.

Insufflation anaesthesia

The ideal anaesthetic technique should be administered without intubation of the larynx so as to optimize the operator's view but maintain adequate ventilation and oxygenation (Johans and

Reichart, 1984). Insufflation anaesthesia fulfils this criterion and is a simple technique. Potential problems associated with the use of a pharyngeal catheter can be avoided by the use of modified metal instruments such as laryngoscopes and anterior commisure retractors, the suction channel of which can be used as a conduit for anaesthetic gases.

The technique provides moderately deep anaesthesia with spontaneous ventilation and less anaesthetic equipment in the airway. The responsibility of maintaining an unobstructed airway lies with the operator. An inhalation induction with oxygen, air and a volatile agent to a depth adequate to obtund laryngeal reflexes, is followed by a thorough spraying of the airway with 1% lignocaine. Brummitt, Fearon and Brauma (1981) have suggested that supplementation with methoxyflurane provides excellent analgesia and good neuromuscular blockade without ventilatory depression or explosive risks. A slow recovery time and dose-related renal toxicity suggest exposure to the drug be limited. The gas flow required to maintain a normal carbon dioxide tension is twice the patient's calculated minute volume.

Although this technique is not innocuous, it is appropriate for laser surgery of the infant larynx. Tracheal tubes obstruct the operating field in infants and small children, especially those with subglottic stenosis. During spontaneous ventilation, the vocal cords are in motion, which is inappropriate for laser laryngoscopy. The depth of anaesthesia may be decreased if not enough gas is used or too much is removed by suction, leading to awakening, laryngospasm or varying degrees of hypoxia. Operating room pollution from anaesthetic vapours and smoke is high. The use of suction and scavenging devices will reduce this problem. The technique also leaves the airway open to soiling from debris and blood.

ANAESTHESIA FOR TRACHEOBRONCHIAL LASER SURGERY

Patients presenting for tracheobronchial laser surgery have varying degrees of ventilatory obstruction. The use of a carbon dioxide laser for benign tracheal strictures appears to produce unsatisfactory results unless combined with the use of tracheal stents.

Until recently, radiation therapy, direct piecemeal removal with a forceps, electrocoagulation and cryosurgery were the only forms of treatment available for tracheobronchial neoplasms. Nonresectable intraluminal lesions of the trachea and mainstem bronchi are more treatable with lasers as a result of advances in technology. The use of lasers in neoplastic lesions is essentially palliative and is used as a debulking tool before radiotherapy.

Anaesthesia for tracheobronchial laser surgery presents problems different from those of laryngeal surgery. The fear of fire hazards is minimal, as the anaesthetic conduit consists of a fire-resistant metal bronchoscope. More important is the problem of high airway impedence distal to the point of gas delivery, and the difficulty of maintaining adequate alveolar ventilation.

Sanders' technique of manually controlled ventilation using the venturi through an open-ended bronchoscope is that of choice for routine rigid bronchoscopy. The use of this technique in carbon dioxide laser bronchoscopy is not practical, as the operator end of the bronchoscope is wholly occupied by the laser manipulator, thus reducing the availability of air for entrainment. The ability of the venturi device to entrain is further reduced by the decrease in lung compliance and increase in airways resistance which are common in these patients. Prolonging the inspiratory time does not increase the tidal volume, but achieves a better distribution of gases within the lung (Jardine, Harrison and Healy, 1975). In practice, it is better to use a short inspiratory period followed by a long expiration.

Smoke produced in the tracheobronchial tree obstructs the operator's view. The use of high gas flows through the bronchoscope disperses the smoke distally into the alveoli as well as to the external environment. Prevention of alveolar pollution by smoke is difficult and requires the incorporation of a scavenging system. Synchronized suction with ventilation is difficult to achieve, but taking turns at the airway using alternate periods of suction–vaporization and ventilation appears to be more successful in reducing alveolar pollution (Conacher, Paes and Morritt, 1985; Paes, Conacher and Snellgrove, 1986).

Malignant growths tend to be friable and bleed easily during instrumentation. Application to the site of cotton swabs soaked in 1% adrenaline may reduce bleeding. Treatment of malignant tumours with radiotherapy increases their size and vascularity. This may tip some patients into ventilatory failure. The increased vascularity makes laser vaporization difficult, as blood splatters onto the optical system and light source. Debulking of the tumour by laser therapy followed by radiotherapy is to be preferred.

There is debate about the advisability of recanalizing totally obstructed main bronchi because, in many patients, it has been found that there is no useful gain in lung function, although the feeling of dyspnoea is diminished. Problems may occur when an obstructed main bronchus is recanalized, exposing the normal lung to the potentially infected contents of the obstructed one. Bronchoscopic clearance of the affected lung must be carried out diligently following recanalization.

Anaesthetic techniques for tracheobronchial laser surgery

The duration of this procedure varies from 30 min to 2 h. Anaesthesia is induced in the conventional manner using thiopentone and a single dose of suxamethonium to introduce the bronchoscope. The tracheobronchial tree is examined without touching the lesion—which invariably bleeds on handling. The difficulty of ventilation can be assessed at this examination. Large tracheal or tracheobronchial tumours will require high ventilatory pressures, whereas those in the main bronchus rarely do. A tendency to intubate the affected bronchus reduces ventilation considerably. The effects of this can be minimized by having additional openings at the distal end of the bronchoscope through which gas can escape to ventilate the normal lung. Alternately, the bronchoscope can be withdrawn into the trachea during the ventilation period.

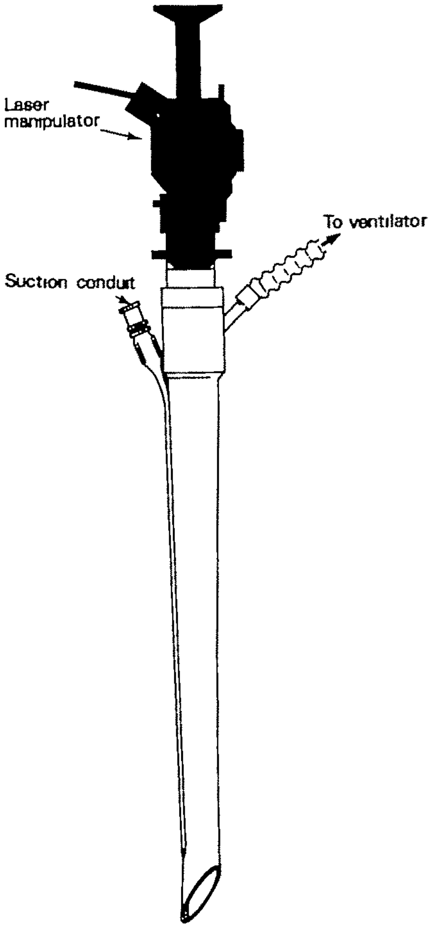

FIG. 2. Ventilating bronchoscope.

There are essentially two methods of maintaining anaesthesia in these patients during vaporization:

(A) An anaesthetic circuit is connected to the ventilation port of the ventilating bronchoscope and a gas mixture of oxygen, air and a volatile agent is transmitted to the patient (fig. 2). A high gas flow is necessary to compensate for the leak between the bronchoscope and the trachea, as well as to disperse the smoke away from the site. A Foregger cuff can be added to the bronchoscope to prevent the gas leak, but the operator's vision may be less than ideal with the smoke swirling in the bronchoscope. Spontaneous ventilation is contraindicated because of the duration of the procedure and the high respiratory workload borne by the patient. Mechanical ventilation must be used.

Smoke pollution of the alveoli is usually high as vaporization and ventilation are carried out simultaneously. Suction can be applied using the suction conduit available on some bronchoscopes. "Flaring" of carbonized particles is common as laser vaporization is performed continuously over a prolonged period. The procedure is usually interrupted at varying intervals so that carbonized debris can be removed from the site.

(B) Jet ventilation using a needle device at the ventilation port of the ventilating bronchoscope is an alternative and possibly better technique. A 14-gauge needle for adults and a 16-gauge needle for children should be adequate (fig. 3). Ventilation is performed at the same time as vaporization. Anaesthesia is maintained by a continuous i.v. infusion of an appropriate anaesthetic drug or drugs. The circulatory response to endoscopic instrumentation should be obtunded, by the use

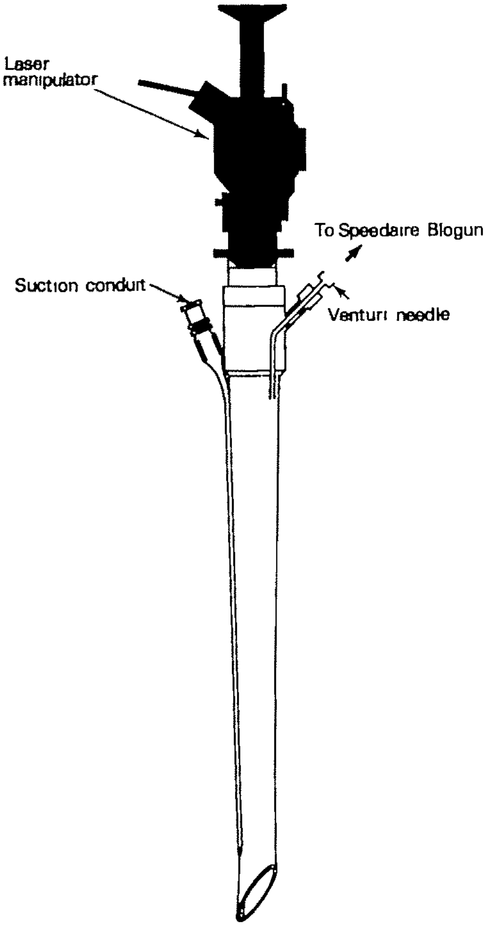

FIG. 3. Ventilating bronchoscope with venturi needle.

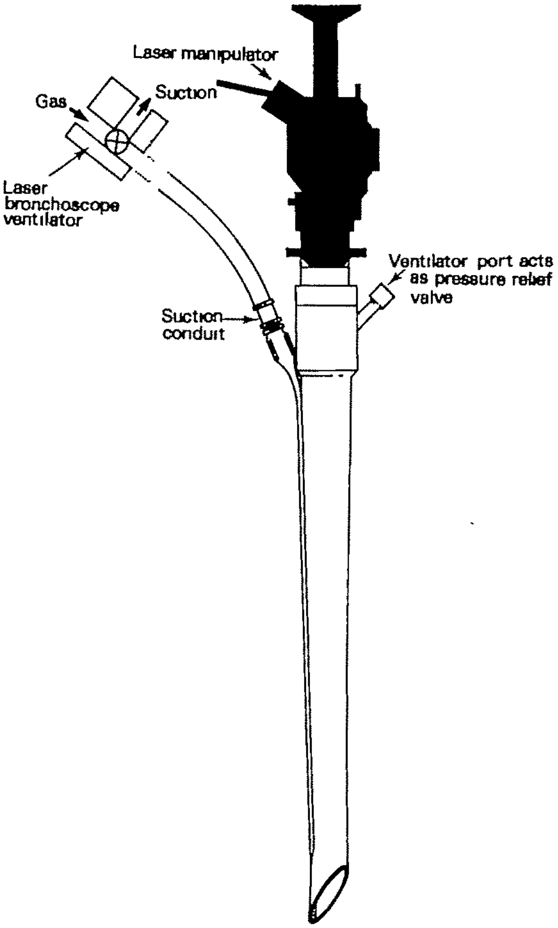
Laser manipulator
Gas
Suction
Laser bronchoscope ventilator
Ventilator port acts as pressure relief valve
Suction conduit

FIG. 4. Ventilating bronchoscope with laser bronchoscope ventilator.

of short acting analgesic agents and vasodilator therapy.

A variation of the above technique is used by the author's team. The suction channel is used as a common conduit for ventilation and suction (figs 4, 5). A system of taking turns at a shared airway, whereby periods of ventilation are alternated with periods of suction, is used. This is achieved either manually or by the use of a laser bronchoscope ventilator, permitting the operator to vaporize only during the suction phase (Conacher, Paes and Morritt, 1985; Paes, Conacher and Snellgrove, 1986). The ventilator provides a period of apnoea with a quiescent operating field for vaporization, extracts a large amount of smoke and then switches over to the ventilatory phase. Jet ventilation can also be applied using a needle device at the ventilator port and suction through the suction conduit. The laser bronchoscope ventilator can still be used to alternate the two functions. An integral part of the technique is serial monitoring of arterial blood-gas tensions. This has enabled the arterial oxygen and carbon dioxide tensions to be maintained at normal values, by adjusting the technique as necessary.

This technique provides a quiescent period for vaporization and minimizes smoke pollution. The incidence of flaring is low, as the oxygen concentration decreases during the suction–vaporization phase and the soot particles have cooled during the previous ventilation cycle. The procedure takes a little longer than one in which laser vaporization is peformed continuously.

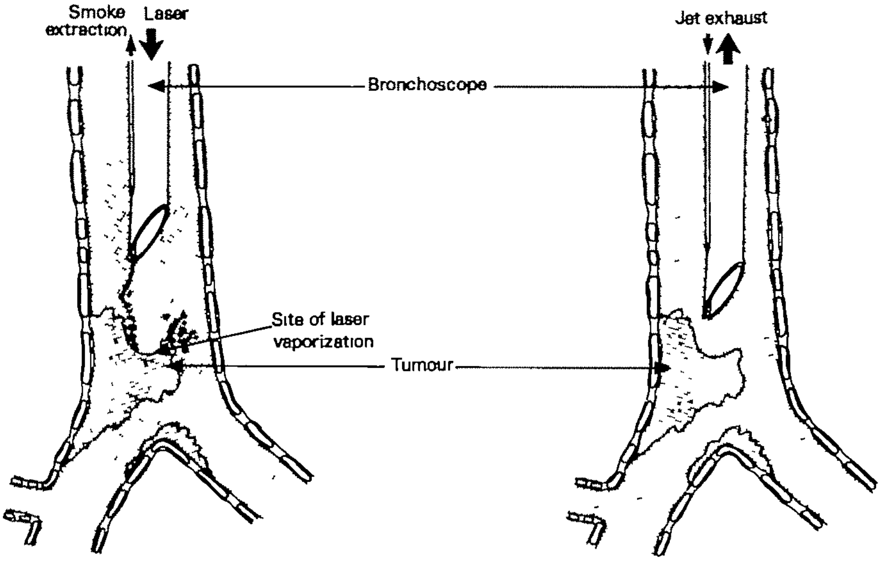

FIG. 5. Taking turns at the airway.

CONCLUSION

The use of lasers in the airway provides precise, bloodless surgery which is painfree and devoid of tissue oedema. The dangers associated with their use in the airway relate mainly to fire hazards in upper airway surgery and to the maintenance of adequate ventilation in lower airway surgery.

A number of features are essential in good practice for laser surgery. A team should be familiar with the problems of lasers in the airway, have good co-operation and communication with each other, and maintain constant vigilance. Adequate instrumentation should be available to allow the use of alternative techniques and comprehensive monitoring is valuable in difficult situations. Finally, a disaster "drill" should be devised and rehearsed by all members of the team.

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COMPARISON OF PHYSICAL AND FLOW CHARACTERISTICS OF "STREAMLINE" AND "NORMAL" CUFFED TRACHEAL TUBES

G. N. KALLA AND J. VENKATARAMANA

SUMMARY

A comparative study was undertaken of the physical and flow characteristics of "streamline" cuffed tracheal tubes (SCT; Medishield) and "normal" cuffed tracheal tubes (NCT) of sizes 6.0, 6.5, and 9.0 mm. The embedding of the pilot tube within the wall of SCT imparts a D-shaped lumen which is more marked in 6.0- and 6.5-mm tubes. As a result, there is a 15% reduction in the lumen of a 6.5-mm SCT. All sizes of SCT studied had a smaller outer diameter compared with the corresponding sizes of NCT and thus occupied less space in the trachea. In sizes 6.0 and 6.5 mm, the SCT was found to have distinct disadvantages, such as increased resistance to ventilation of up to twice that of NCT, and turbulent flow even at a minute volume of 5 litre min^{-1}. SCT, size 9.0 mm, however offered marginally less resistance compared with NCT of the same size.

The "streamline" cuffed tracheal tube (SCT; Medishield) is different in design compared with "normal" cuffed tracheal tubes (NCT) from the same and other manufacturers. The difference is that the embedding of the pilot tube in the wall of the SCT causes a bulge within the lumen, thus reducing the cross-sectional area. Figure 1 compares the shapes of the lumena and the positioning of the pilot tubes.

The use of a 6.5-mm SCT in a young Nigerian female patient resulted in increased ventilatory resistance. This was severe enough to require verification of the placement of the tracheal tube and to warrant a search of the entire breathing system for any kink or other form of obstruction. No fault was found in the breathing system or in the placement of the tracheal tube and it was decided to change the tube. The inflation of the lungs became easy after replacing the SCT by an NCT of the same size. Thus it was decided to undertake a comparative study of the physical and flow characteristics of SCT and NCT tubes.

MATERIALS AND METHODS

Five normal and five streamline cuffed red rubber tracheal tubes, of each of the sizes 6.0, 6.5 and 9.0 mm, undistorted by connector were studied (table I). All the measurements were made on an undistorted section of each tube.

In an unused tracheal tube the dimensions of the proximal end of the tube should be as specified by the manufacturer, but, in a used tube, owing to the connector being thrust in and left *in situ* at the proximal end, some dilatation, giving erroneously higher values, can be expected. To avoid this possible source of error, measurements were made of an undistorted section of each tube. The proximal end of each tube was cut 1 cm below the estimated length of a typical connector in both used and unused tubes to obtain an unaffected section.

Physical dimensions

The following measurements were made on the NCT at 24 °C (fig. 2): external diameter (*Do*); external diameter of the cuffed portion of tube

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G. N. KALLA,* M.B., B.S., M.D. (A.I.I.M.S.), Department of Anaesthesiology, College of Medical Sciences, University of Benin, Benin City, Nigeria. J. VENKATARAMANA, PH.D., Department of Civil Engineering, Faculty of Engineering, University of Benin, Benin City, Nigeria. Accepted for Publication: June 1, 1987.

*Present address: Department of Anaesthetics, King George Hospital, Eastern Avenue, Newbury Park, Ilford IG2 7RL.

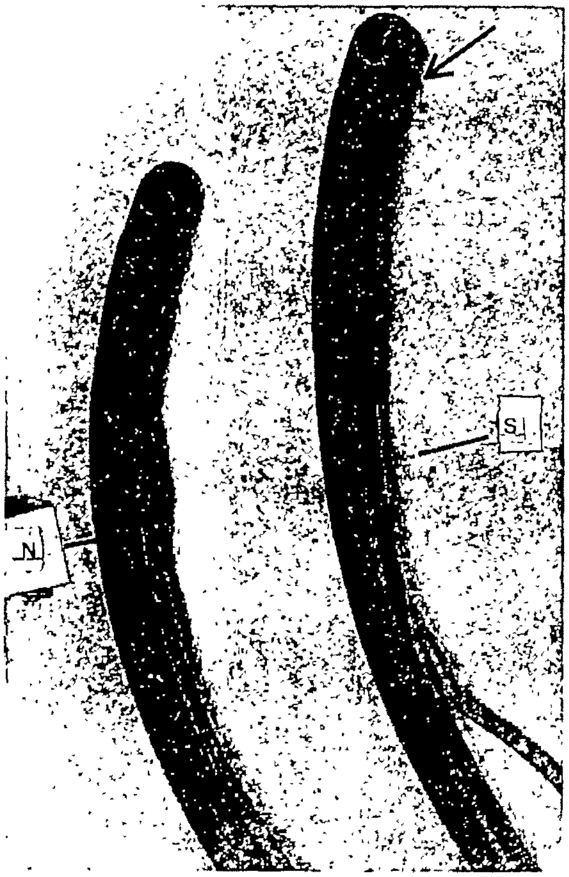

FIG. 1. Photograph of 6.5-mm SCT and NCT. Note the shapes of the lumena and the point of emergence of the pilot tubes.

TABLE I. *Cuffed tracheal tubes studied (all Red-rubber). Physical characteristics: manufacturing data*

Manufacturer	Indicated size (mm)	Type of tube
Franklin	6.0	NCT
Medishield BOC	6.0	SCT
Franklin	6.5	NCT
Medishield BOC	6.5	SCT
Medishield BOC	9.0	NCT
Medishield BOC	9.0	SCT

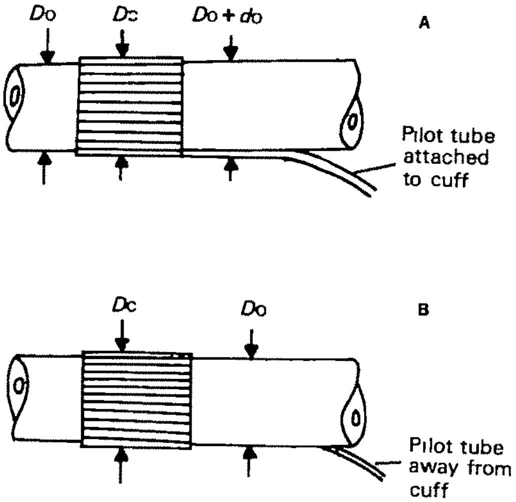

FIG. 2. Physical dimensions of NCT (A) and SCT (B) *Do* = External diameter; *Dc* = external diameter of cuffed portion; *do* = diameter of pilot tube.

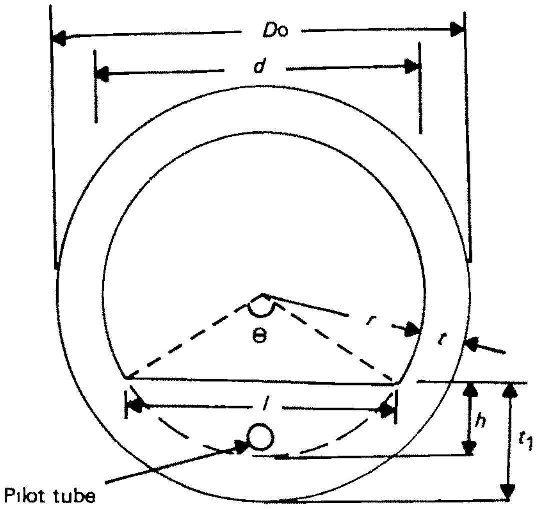

FIG. 3. Cross section of an SCT. *Do* = External diameter; *d* = internal diameter; *r* = internal radius; *t* = thickness of annular portion of tube; t_1 = maximum thickness of bulge in the tube lumen where pilot tube is embedded; $h = t_1 - t$; *l* = length of chord representing bulge in lumen; θ = angle subtended by the chord at the centre of the lumen.

(*Dc*); diameter of the pilot tube (*do*); combined external diameter of tracheal tube + pilot tube (*Do* + *do*); internal diameter of the tube (*d*) (= (*Do* − 2*t*), in which *t* is the thickness of the annular portion of tube (fig. 3)). The thickness of the cuff (*tc*) was calculated as *tc* = (*Dc* − *Do*)/2.

The following measurements were made on the SCT at 24 °C (figs 2, 3): external diameter (*Do*); external diameter of cuffed portion of tube (*Dc*); internal diameter of the annular portion of the tube lumen (*d*); thickness of the annular portion of the lumen (*t*); maximum thickness of bulge in the tube lumen where pilot tube is embedded (t_1); length of the chord (*l*). The diameters were measured using a micrometer screw gauge and the thickness of the wall was measured with a slide caliper.

Flow characteristics

The cross-sectional area, hydraulic radius, effective internal diameter, Reynold's number and resistance to gas flow were calculated for each of the tubes separately at 24 °C to obtain the flow characteristics.

Reynold's number. For a fluid flowing through a long tube under steady conditions, the Reynold's number, which is a non-dimensional quantity, is given by

$$Re = \frac{dV}{\eta/\rho} \tag{1}$$

where d = internal diameter of the tube at the plane of cross-section; V = average velocity; ρ = density of the fluid; η = absolute viscosity of the fluid (η/ρ = kinematic viscosity).

Reynold's number indicates whether the flow is laminar, turbulent or mixed.

For an annular tube, under constant flow rate $\dot{v}$,

$$\dot{v} = \frac{\pi d^2}{4} V$$

Substituting this in equation (1) we get

$$Re = \frac{4\dot{v}}{\pi d(\eta/\rho)} \tag{2}$$

This equation can be used directly to calculate the Reynold's number for NCT. However, for SCT the cross section is non-annular and D-shaped. Hence, an equivalent diameter must be defined before using equation (2). This is done as follows. In figure 3, the chord length (l) and angle θ (the angle subtended at the centre) can be calculated using simple geometry. In a right-angled triangle:

$$(\tfrac{l}{2})^2 = (\tfrac{d}{2})^2 - (\tfrac{d}{2} - h)^2$$

from which, on simplification we get:

$$l = 2\sqrt{h(d-h)} \tag{3}$$

where $h = t_1 - t$.

Also,

$$\cos\left(\frac{\theta}{2}\right) = \frac{d/2 - h}{d/2}$$

or

$$\theta = 2\cos^{-1}\left(1 - \frac{2h}{d}\right) \tag{4}$$

Area of segment (Beyer, 1978) is given by

$$\frac{d^2}{8}\left(\frac{\theta\pi}{180} - \sin\theta\right)$$

Therefore, the area of the D-shaped lumen is given by

$$A = \frac{\pi d^2}{4} - \frac{d^2}{8}\left(\frac{\theta\pi}{180} - \sin\theta\right) \tag{5}$$

The wetted perimeter (P) is given by

$$P = \pi d\left(1 - \frac{\theta}{360}\right) + l \tag{6}$$

where wetted perimeter is the perimeter of the tube which is in contact with the fluid/gas. The hydraulic radius (R) (Streeter and Wylie, 1971) is defined as:

$$R = \frac{\text{cross-sectional area}}{\text{wetted perimeter}} = \frac{A}{P} \tag{7}$$

For a circular lumen

$$R = \frac{d}{4}$$

whence, effective internal diameter can be defined as

$$de = 4 \times R \tag{8}$$

In the present study, effective internal diameter and a minute volume of 5 litre min^{-1} were used for the calculation of Reynold's number. For a minute volume of 4 litre min^{-1} and a typical waveform of an anaesthesized patient breathing spontaneously, the mean inspiratory flow rate ($\dot{v}$) is 13.3 litre min^{-1} (Nunn, 1975). Hence, mean inspiratory flow rate for a minute volume of 5 litre min^{-1} equals $13.3 \times 5/4 = 16.625$ litre min^{-1} = 277×10^3 ml s^{-1}.

Kinematic viscosity (η/ρ) of a gas mixture depends on temperature. It is generally agreed that the anaesthetic gas mixture assumes the room temperature of 24 °C. Kinematic viscosity of air is 1.7×10^{-5} m^2 s^{-1} and that of a mixture of 70% nitrous oxide and 30% oxygen relative to air is 1/1.59 (Nunn, 1975). Therefore, the kinematic viscosity of anaesthetic gas mixture of 70% nitrous oxide: 30% oxygen would be $1/1.59 \times 1.7 \times 10^{-5}$ m^2 s^{-1} = 1.07×10^{-5} m^{-2} s^{-1}.

Resistance to gas flow. Hagan–Poiseuille's equation (Comroe et al., 1973) for resistance to laminar gas flow is given by:

$$\text{Resistance} = \frac{8 \times \text{length of tube} \times \text{gas viscosity}}{\pi \times (\text{radius of tube})^4}$$

For the same length of tube and identical gas

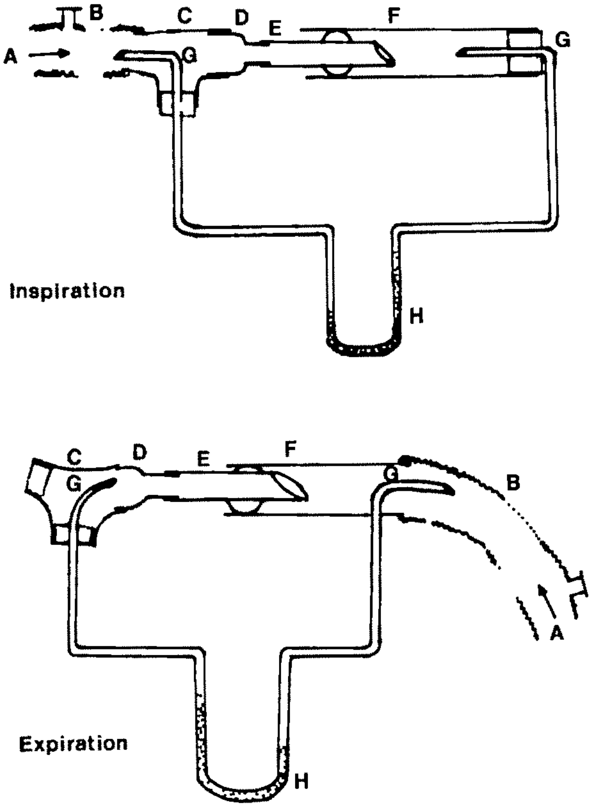

FIG. 4. Schematic layout of the experiment to measure the resistance in NCT and SCT. A = measured flow of gas; B = approximately 1-m length of corrugated tubing; C = Y-connector of circle system; D = tracheal tube connector; E = tracheal tube; F = length of tubing of 15 mm diameter to represent the trachea; G = narrow bore needles pointing upstream; H = U-tube water manometer.

mixture, the resistance for laminar flow (ζ_1) is expressed as

$$\zeta_1 = K_1/(de)^4$$

where K_1 is constant for a given length of the tube carrying a particular gas mixture and de is effective internal diameter. For turbulent flow the resistance (ξ_2) is given by the Fanning equation (Nunn, 1975):

$$\xi_2 = K_2/(de)^5$$

where K_2 is constant.

Plan of investigation

The measurement of resistance was undertaken in each of the three sizes of NCT and SCT by using a U-tube water manometer (fig. 4). Figure 4 depicts the arrangement in the inspiratory phase and in the expiratory phase. The resistance was measured using a fresh gas flow of 5 litre min^{-1}, which equals a mean inspiratory flow of 16.625 litre min^{-1}, consisting of 70% nitrous oxide plus 30% oxygen. This study compared the total resistance of tracheal tube and connector, including the effects of any extra turbulence at each end. The same fresh gas flow was used during inspiration and expiration, to simulate the real clinical situation. The expiratory valve, as used in clinical practice with a Bain circuit, was included to allow the gases to escape during expiration.

Hypothetical calculations

At the conclusion of this study, when it become evident that size SCT 9.0 mm offered less resistance than NCT 9.0 mm, the interrelationship of length of chord (l), internal diameter (d) and the angle (θ) of SCT 9.0 mm were analysed. The l:d ratio of SCT 9.0 mm was calculated then, keeping this ratio fixed for SCT 6.0 and 6.5 mm, the assumed values for l, d and θ were transposed to

TABLE II. *Physical characteristics of cuffed tracheal tubes studied: mean dimensions (mm).* Do = *External diameter*; Dc = *external diameter of cuffed portion*; do = *diameter of pilot tube*; d = *internal diameter*; t_1 = *maximum thickness of bulge in tube lumen where pilot tube is embedded;* t = *thickness of annular portion of tube*; tc = *thickness of cuff*; l = *length of chord (values in parentheses based on equation (3), without parentheses are actual measurements)*

Tube type and size (mm)	*Do*	*Dc*	*Do+do*	*d*	t_1	*t*	*tc*	*l*	θ°
NCT 6.0	8.80	9.52	11.30	6.30	—	1.25	0.36	—	—
SCT 6.0	9.10	9.50	—	6.58	3.42	1.21	0.20	6.26 (6.21)	141.67
NCT 6.5	9.02	10.16	11.65	6.60	—	1.21	0.57	—	—
SCT 6.5	9.54	10.26	—	6.96	3.30	1.29	0.36	6.42 (6.31)	130.02
NCT 9.0	12.64	12.98	15.05	9.24	—	1.70	0.17	—	—
SCT 9.0	13.20	13.80	—	9.90	2.06	1.65	0.30	4.16 (3.95)	46.96

TABLE III. *Flow characteristics of cuffed tracheal tubes studied.* Re *has been calculated for a mean inspiratory flow of 16.625 litre min*$^{-1}$

Tube type and size (mm)	Cross-sectional area *A* (mm^2)	Wetted perimeter *P* (mm)	Hydraulic radius *R* (mm)	Effective internal diameter *de* (mm)	Reynold's number *Re*
NCT 6.0	31.17	19.79	1.58	6.30	5232
SCT 6.0	23.98	18.80	1.28	5.12	6438
NCT 6.5	34.20	20.70	1.60	6.60	4994
SCT 6.5	28.94	20.28	1.43	5.72	5762
NCT 9.0	67.06	29.03	2.31	9.24	3567
SCT 9.0	75.89	30.99	2.45	9.80	3363

TABLE IV. *Flow characteristics of cuffed tracheal tubes studied: comparison of resistances to gas flow*

Tube type and size (mm)	Effective internal diameter *de* (mm)	Fanning equation $(de)^5$ (mm)	Resistance at 5 litre min^{-1} flow ξ/K (mm)^5	Ratio of resistance in SCT:NCT at 5 litre min^{-1}
NCT 6.0	6.30	0.9924×10^4	1.008×10^{-4}	2.61
SCT 6.0	5.20	0.3802×10^4	2.63×10^{-4}	
NCT 6.5	6.60	1.2523×10^4	0.799×10^{-4}	2.04
SCT 6.5	5.72	0.6123×10^4	1.633×10^{-4}	
NCT 9.0	9.24	6.7353×10^4	0.148×10^{-4}	0.75
SCT 9.0	9.80	0.9039×10^4	0.111×10^{-4}	

other actual measurements of SCT of these sizes for the calculations of Reynold's number.

RESULTS

Table II gives all the dimensions of these tubes. Table III gives cross sectional area (*A*), wetted perimeter (*P*), hydraulic radius (*R*), effective internal diameter (*de*) and Reynold's number (*Re*) calculated for all tubes. Table IV compares the resistance to gas flow in these tubes. Table V shows experimental measurements and comparison of resistances in NCT and SCT. Table VI gives hypothetical calculations of *Re* in SCT 6.0 and 6.5 mm, with assumed values of *l*, *d* and *θ*. The accurate measurement of length of chord (*l*) in SCT was found to be difficult and so the calculated values of *l* were used. However, for the

TABLE V. *Flow characteristics of cuffed tracheal tubes studied: experimental comparison of resistance at a steady flow of 5 litre* min^{-1}

Tube type and size (mm)	Pressure decrease during		Ratio of resistance (NCT:SCT)
	Inspiration (mm H_2O)	Expiration (mm H_2O)	
NCT 6.0	7	6	
SCT 6.0	14	7	1.0:2.0
NCT 6.5	11	9	
SCT 6.5	17	9	1.0:1.6
NCT 9.0	14	9	
SCT 9.0	13	10	1.0:0.93

TABLE VI. *Flow characteristics of cuffed tracheal tubes studied: Hypothetical calculations in SCT. *Actual values, from table II*

Tube size (mm)	Length of chord (l) (mm)	Internal diameter (d) (mm)	Angle ($\theta°$)	Ratio $l:d$	Reynolds's number (Re)	Resistance ξ/K
9.0*	3.95	9.90	46.96	0.4	3363	0.111×10^{-4}
6.5	2.784	6.96	47.00	0.4	4791	0.647×10^{-4}
6.0	2.665	6.68	47.00	0.4	4987	0.793×10^{-4}

sake of clarity both calculated and measured values of l have been included in table II.

By substracting Dc of SCT from $Do + do$ of the NCT of the same size, the extra space the NCT would occupy in the glottis can be calculated. NCT compared with the SCT occupied 18.95%, 13.55% and 9.06% for sizes 6.0, 6.5 and 9.0 mm, respectively. In sizes 6.0 and 6.5 mm, the cuff thickness was 0.32 and 0.42 mm more in SCT than in NCT, respectively. The internal diameter (d) of the circular portion of SCT was appreciably larger than that of NCT.

The effective internal diameter was found to be larger than the indicated tube size in all the three sizes of NCT studied, whereas it was less in SCT 6.0 and 6.5 mm. In SCT 9.0 mm *Re* was less than that of NCT 9.0 mm. SCT 6.0 mm had the largest *Re*.

DISCUSSION

After intubation of the trachea, the tracheal tube and its pilot tube together occupy a certain volume in the glottis. From the present study, it is evident that, when an SCT is used, less outer diameter is occupied compared with an NCT. This difference decreases as the size of the tube increases. This, probably, is the single advantage SCT 6.0 and 6.5 mm offer over NCT.

Determination of *Re*, for calculating resistance to gas flow, requires measurement of the internal diameter of the tracheal tubes. Diameter can be measured in a tube with a circular shaped lumen, but not in one with a non-circular shaped lumen such as the SCT. The hydraulic radius permits circular and non-circular sections to be treated similarly for calculation of fluid mechanics (Streeter and Wylie, 1971). Effective internal diameter is calculated from hydraulic radius. It is suggested that the effective internal diameter is the comparable measurement in both NCT and SCT. Therefore it, instead of simple diameter, should be used in the calculation of Reynold's number, when comparing NCT and SCT. Although the internal diameter of the circular portion of SCT is larger than that of NCT, it is not adequate to prevent an increase in resistance to gas flow.

The Reynold's number (*Re*) indicates whether flow would be laminar, turbulent or mixed. The critical Reynold's number (*Rec*) refers to the condition of initiation of turbulence and not to a situation where the flow is fully turbulent. Most authorities agree that, at *Rec* 2000, the flow would become turbulent (Streeter and Wylie (1971)—quoting original experiments of Reynold (1883) McDonald (1960), Hill (1976) and Atkinson, Rushman and Lee (1982)), whereas Coulter and

Pappenheimer (1949) and Nunn (1975), quoting the work of Cooper, suggested the value of *Rec* to be 1000. The Reynold's number is a constant and it is not desirable to replace diameter for radius in Reynold's original equation, because radius is not a measured quantity; it is the diameter which is measured. The use of radius instead of diameter can erroneously reduce the value of *Rec* to half the actual value, 1000 in the present case.

Rec may also depend on the roughness of the material of the tube, changes in the cross-sectional area of tube, whether the tube is straight or branched, and on the initial condition of flow before entering the tube. The tube material and the initial condition of flow before entering the tube can be taken as constant in the present comparison. There was no branching in the tubes. The pilot tube is a blind tube connected to the cuff and does not take part in the gas flow through tracheal tube. The bulge in the lumen of SCT brings about a change in cross-sectional area, adversely affecting *Rec*. It is, therefore, evident that change of shape of the lumen from annular to D-shaped and the incorporation of sharp angles, increase the resistance and turbulence in the flow. The Fanning equation (Nunn, 1975) states that, for turbulent flow, the resistance is inversely proportional to the 5th power of diameter. It is evident, therefore, that a small decrease in effective internal diameter would result in a disproportionately greater increase in the resistance, especially if the flow were turbulent.

The effective internal diameter in SCT 6.0 and 6.5 mm has been found to be less than the effective internal diameter of NCT of similar sizes. Correspondingly, *Re* was found to be larger and the resistance to gas flow was increased in SCT 6.0 and 6.5 mm.

The resistance to gas flow for both laminar and turbulent flow, was found to be greater in SCT 6.0 and 6.5 mm compared with NCT of same sizes. The increase in resistance was the highest in SCT size 6.0 mm. In SCT 6.0 and 6.5 mm, the ratio of resistance increased to more than twice that of NCT for turbulent flow. The decrease in resistance was seen in only size 9.0 mm of SCT: the ratio of resistance decreased to 0.75 for turbulent flow. The measurements of undistorted sections of the tracheal tubes were identical in all the tubes; hence, statistical analysis of results was not required.

The ratio of resistance measured experimentally during inspiration (NCT:SCT) was 1:2 for 6.0 mm, 1:1.6 for 6.5 mm, and 1:0.93 for the 9.0 mm-size, whereas the ratio during the expiratory phase was nearly unity. The experimental resistance ratios can be expected to be nearer to unity than the theorectical ones, because they include relatively constant end-effects. However, we are unable, for the present, to offer any satisfactory explanation for the high inspiratory resistance measured experimentally in 6.0- and 6.5-mm SCT. The resistance measured during the inspiratory phase in all the sizes and types of the tracheal tubes was always more than that during expiration—which is considered to be a passive phenomenon. This perhaps is the reason why inspiratory resistance was found to be more than expiratory resistance in all the types and sizes of tracheal tubes studied.

SCT size 9.0 mm has advantages over NCT 9.0 mm as it offers marginally less resistance while retaining the other advantage of the other sizes—occupying less space in the glottis. It is thus, hypothetically, suggested that the l:d (length of the chord : internal diameter) ratio of SCT size 9.0 mm should be taken as the ideal ratio for SCT of all sizes. The hypothetical calculations with assumed values of l, d, and θ in SCT of 6.0- and 6.5-mm size, while maintaining the ideal ratio of l/d, reveal a decrease in resistance and Reynold's number. This perhaps suggests that the diameter of pilot tube embedded within the wall of SCT should be reduced, which in turn would increase the resistance during cuff inflation. However, increased resistance experienced by the anaesthetist in inflating the cuff will not be detrimental to the patient. It remains to be ascertained if this suggestion is compatible with the present manufacturing process of SCT.

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ANAESTHESIA FOR MAJOR ABDOMINAL SURGERY IN A PATIENT WITH MYOTONIA DYSTROPHICA

J. CASTANO AND N. PARES

SUMMARY

A case report is presented of a woman with known myotonia dystrophica, who required partial gastric resection and cholecystectomy. Neuromuscular blockade was obtained using a single dose of vecuronium, and neuromuscular function was determined by the "train-of-four count" technique. The intraoperative course was uneventful, and it was not necessary to use neostigmine to antagonize neuromuscular blockade at the end of the operation. There were no postoperative complications and the patient was discharged from hospital 10 days later.

Myotonia dystrophica is a hereditary disease which may present serious problems for the anaesthetist. It is characterized mainly by myotonia and muscular wasting (Miller and Lee, 1981). Myotonia may be provoked by suxamethonium, neostigmine, hypothermia, shivering or hyperkalaemia, and may render ventilation difficult and tracheal intubation impossible.

Patients are sensitive to barbiturates, opioids, benzodiazepines and volatile agents, all of which may cause apnoea when administered in small doses. These and other anaesthetic problems have been reviewed by Aldridge (1985).

We present a patient suffering from all of the typical signs and symptoms of the disease, who was successfully managed while undergoing an urgent partial gastrectomy.

CASE REPORT

The patient was a 50-yr-old woman. Her mother had died 10 years earlier following the administration of suxamethonium for an orthopaedic operation; her aunt had suffered from myotonia, but her father and brother are fit and well.

At the age of 10 yr the patient underwent an uneventful tonsillectomy. The first symptoms of myotonia dystrophica appeared at the age of 20 yr, with dysarthria, atrophy of the extremities and myotonia in both hands. The patient also complained of difficulties with mastication and in lifting her head while supine. She later developed frontal baldness, inexpressive facies, mental retardation and inability to walk more than a short distance (grade III myotonia) (Gillam et al., 1964).

During the 15 years before admission she had suffered from recurrent biliary colic, but always refused surgery. However, a recently diagnosed gastric carcinoma *in situ* made surgery imperative.

Preoperative assessment

Laboratory findings were normal. A chest radiograph showed a normal sized heart, but atelectasis of the lower lobe of the left lung. Pulmonary function tests indicated moderate airway restriction. The ECG showed some characteristics typical of the disease: P–R 200 ms, Q waves, and an incomplete right bundle branch block.

Bearing in mind the tragic death of her mother, the patient refused a general anaesthetic initially. She even asked for acupunture and other alternative techniques. However, following good psychological preparation, she accepted general anaesthesia.

J. CASTANO, M.D. D.A. (ENG.); N. PARES, M.D.; Servicio de Anestesiologia, Reanimacion y Terapeutica del Dolor, Hospital General Mare de Deu de l'Esperanca, Unitat Docent-Facultat de Medicina, Universitat Autonoma de Barcelona, Sant Josep de la Muntaya, 12, 08024 Barcelona, Spain. Accepted for Publication: July 10, 1987.

Intra- and postoperative periods

The patient was not premedicated. ECG, arterial pressure, heart rate, CVP, oesophageal temperature and urinary output were monitored during the operation. A "sleep" dose of thiopentone (240 mg) was administered, followed by vecuronium 6 mg. After 2 min of manual ventilation of the lungs with 100 % oxygen, the trachea was intubated easily. Anaesthesia was maintained with 70 % nitrous oxide in oxygen, supplemented with 0.5 % halothane. Ventilation was controlled mechanically (Engstrom 300 ventilator). Pa_{O_2}, pH, $P{CO_2}$ and electrolyte concentrations were maintained within normal limits.

Neuromuscular function was monitored using a "Myotex" peripheral nerve stimulator, delivering a train of four stimuli at 2 Hz every 12 s to the ulnar nerve via cutaneous electrodes. Unfortunately, a twitch analyser was not available, and the extent of neuromuscular blockade was estimated by counting the number of palpable responses following each series of train-of-four stimuli (d'Hollander et al., 1986). Twenty minutes after the administration of vecuronium, the observed number of twitches had recovered to four. However, as operating conditions remained satisfactory, even during peritoneal closure, no further doses of neuromuscular blocking drug were administered during the remainder of the operation (which lasted 3 h).

No other drugs were administered, except fentanyl 0.1 mg given just before the surgical incision. Normovolaemia was maintained by administering concentrated red cells 2 units, physiological saline 1500 ml and 5 % dextrose-in-water 500 ml, all of which had previously been warmed to a temperature of 36 °C.

At the end of the operation halothane was discontinued and 100 % oxygen administered. After several minutes the patient opened her eyes and regained spontaneous breathing. Since there were no signs of residual neuromuscular blockade, the tracheal tube was removed without the prior administration of neostigmine. The patient remained pain-free for several hours after extubation.

With no postoperative complications, she was discharged from hospital 10 days later.

DISCUSSION

This patient presented considerable anaesthetic difficulties because her myotonia dystrophica had reached an advanced stage and she required a major abdominal operation.

Since exaggerated responses to thiopentone, opioids, benzodiazepines and volatile agents have been reported, regional anaesthesia may be preferable when clinically feasible (Wheeler and James, 1979). However, this approach was not considered appropriate for upper abdominal surgery. The chosen technique aimed to avoid those stimuli (chemical, mechanical, electrical, thermal) or drugs which could provoke sustained contractures.

Suxamethonium and neostigmine were contraindicated. Although Azar (1984) has warned that responses to non-depolarizing neuromuscular blockers may be exaggerated, they appeared to be normal in this case.

Similar cases have been reported. Two were managed using atracurium (Bohehimer, Harris and Ward, 1985; Nightingale, Healy and McGuinness, 1985), and another with dantrolene (Phillips et al., 1984). However, vecuronium is particularly free from adverse effects and was considered to be the neuromuscular blocker of choice.

Neuromuscular function monitoring was delayed until tracheal intubation had been accomplished, in order to avoid any possible sustained electrical contraction during incomplete paralysis. The maintenance of good abdominal relaxation for 3 h with a single dose of vecuronium may be related to:

(a) Muscular weakness attributable to the disease itself;

(b) A prolonged effect of the neuromuscular blocker. Although prolongation of effect was not detected with the train-of-four count, this remains a possibility because of the imprecision of that method. It would have been much more satisfactory to have measured the train-of-four ratio.

(c) An exaggerated response to barbiturates, halothane and fentanyl. This possibility appears unlikely in view of the normal rate of recovery from anaesthesia.

In conclusion, a patient with grade III myotonia dystrophica was managed successfully during major surgery by the use of balanced anaesthesia in the form of a small dose of thiopentone, a single dose of vecuronium, plus halothane and fentanyl.

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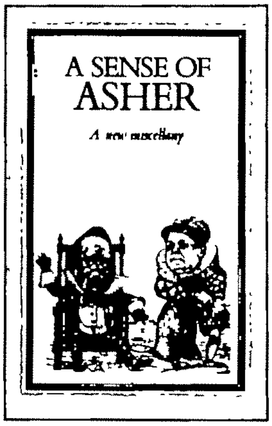

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